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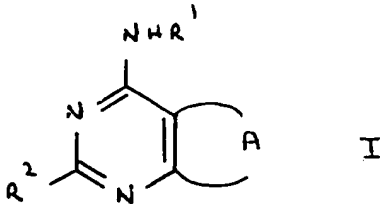
(54) Furyl-substituted purines, oxazolopyrimidines and pteridines as adenosine antagonists.

(57) Compounds of formula I, and pharmaceutically acceptable salts thereof,



I

in which R1 is hydrogen (1-6C)alkyl or (1-4C)alkanoyl ;
A is -N=CQ-O-, N=CQ-NR^8-, -N=CQ-CH=N-
or -N=CH-CQ=N- ;
Q is 2-furyl ;
R^8 is hydrogen or C1-4C)alkyl ;
and R^2 has any of the meanings given in the specification, processes for preparing the compounds and pharmaceutical compositions containing them. The compounds are useful as adenosine antagonists.

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This invention concerns heterocyclic compounds and, more particularly, certain furyl-substituted purines, oxazolopyrimidines and pteridines which have useful pharmacological properties (and in particular antagonise the actions of adenosine such as vasodilation). The invention also includes pharmaceutical compositions containing the heterocyclic compounds for use in treating certain diseases and disorders affecting mammalian cardiac, peripheral and/or cerebral vascular systems. Also included are processes for the manufacture and formulation of the heterocyclic compounds.

The compound theophylline (1,3-dimethylxanthine) has been used clinically (usually as its ethylene diamine salt, which is also known as aminophylline) as a respiratory stimulant, a centrally acting stimulant, a bronchodilator, a cardiac stimulant and as a diuretic. This diversity of clinical uses is an indication of the range of pharmacological actions which have been attributed to theophylline. These include phosphodiesterase inhibition, adenosine receptor antagonism, mobilisation of intracellular calcium and the release of catecholamines. Recently theophylline has also been reported to be useful in treating myocardial ischaemia (Maseri et al., The Lancet, 1989, 683-686), skeletal muscle ischaemia (Picano et al., Angiology, 1989, in press) and cerebral ischaemia (Skinhoj et al., Acta. Neurol. Scand., 1970, 46, 129-140). The beneficial effects of theophylline in these ischaemic disorders are believed to be due to a reduction or prevention of the phenomenon known as "vascular steal" by virtue of the compound's ability to antagonise the actions of adenosine by blocking the adenosine receptors which mediate metabolism-linked vasodilatation.

The "vascular steal" phenomenon can occur when the major artery supplying a particular vascular bed is partially or totally occluded resulting in ischaemia. In this situation, the compromised vascular bed dilates and blood flow is maintained by either an increase in flow across the narrowed vessel or by an increase in flow through the collateral vessels. However, increased metabolic activity in adjacent vascular beds results in release of mediators such as adenosine, causing them to dilate, resulting in the limited blood flow to the compromised vascular bed being "stolen" by these adjacent areas. The loss of blood from compromised to normally perfused vascular beds by the phenomenon of "vascular steal" further diminishes the blood flow in the compromised vascular bed.

The diversity of pharmacological properties possessed by theophylline make it difficult to use in the regular treatment or prevention of occlusive diseases and conditions of the vasculature. Thus, its associated action as a phosphodiesterase inhibitor results in cardiac stimulation which is deleterious for patients with myocardial ischaemia. Furthermore, the relatively low potency of theophylline means that dose-levels which are therapeutically useful are close to those which can cause serious central side-effects.

Several furyl-substituted purine and pteridine compounds are known. El Khadem, H.S. and Sindric, R., Carbohydrate Research, 34, (1974), 203-207 discloses 6-amino-8-(2-furyl)-1H-purine. This compound was obtained as a byproduct during the synthesis of certain 6-amino-8-hydroxyalkyl-1H-purines. The compound 2,4,7-triamino-6-(2-furyl)pteridine (also called furterene) is known as a diuretic.

We have now discovered (and this is a basis for our invention) that a group of furyl-substituted purines, oxazolopyrimidines and pteridines of formula I defined below are effective antagonists of the actions of adenosine and in particular of its vasodilatory actions.

According to the invention there is provided a compound of the formula I set out hereinafter (together with the other formulae appearing in Roman numerals)wherein:

R^1 is hydrogen, (1-6C)alkyl, or (1-4C)alkanoyl;

R^2 is hydrogen, cyano or a group of formula R^3X;

R^3 (when not as hereinbelow defined together with X) is (3-12C)cycloalkyl, (3-6C)alkenyl, phenyl(3-6C)alkenyl, 5- or 6-membered heteroaryl, optionally substituted (1-6C)alkyl or optionally substituted phenyl,

said optionally substituted alkyl being unsubstituted or substituted by one of (3-6C)cycloalkyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted phenyl and a group of formula $R^4(CO)_nX_a(CO)_m$ in which R^4 is (1-6C)alkyl, (3-6C)cycloalkyl, optionally substituted phenyl or optionally substituted phenyl(1-4C)alkyl, n and m are each 0 or 1 provided that n+m is 0 or 1, and that when m is 0, X and X_a are separated by at least two carbon atoms, X_a is oxy, thio, sulphinyl, sulphonyl or an imino group of formula -NRb in which Rb is hydrogen, (1-6C)alkyl or together with R^4 and the adjacent nitrogen atom forms a 4 to 6-membered saturated heterocyclic ring,

said optionally substituted 5- or 6-membered heteroaryl being unsubstituted or substituted by 1 or 2 of (1-4C)alkyl, (1-4C)alkoxy and halogeno,

and any of said optionally substituted phenyl being unsubstituted or substituted by (1-4C)alkylenedioxy or by 1,2 or 3 of halogeno, cyano, trifluoromethyl, (1-4C)alkoxycarbonyl, hydroxy, hydroxymethyl, amino, (1-4C)alkanoylamino, (1-4C)alkoxymethyl, (1-4C)alkanoyloxy, benzyloxy, halogenobenzyloxy, (1-4C)alkylsulphonylamino,

(1-4C)haloalkylsulphonylamino, nitro, and (1-4C)alkyl or alkoxy optionally bearing a group of formula R^5CO in which R^5 is (1-4C)alkoxy, (3-6C)alkylamino, (3-6C)cycloalkylamino or (N-(1-4C)alkyl) (N-(1-4C)dialkylamino(1-

4C)alkyl)amino, and sulphamoyl of formula $-SO_2.NR^6R^7$ in which R^6 and R^7 are independently hydrogen or (1-4C)alkyl, or R^6 is hydrogen and R^7 is ((2-5C)alkoxycarbonyl)$(CH_2)q$-, carbamoyl$(CH_2)q$ or (N-(1-4C)alkylcarbamoyl)$(CH_2)q$, in which q is 0 or an integer of from 1 to 4, or R^6 is (1-4C)alkyl and R^7 is di(1-4C)alkylamino(1-4C)alkyl; and

X is a direct bond or oxy, thio, sulphinyl, sulphonyl or an imino group of formula -NRa- in which Ra is hydrogen, (1-6C)alkyl or together with R^3 and the adjacent nitrogen atom forms a 4 to 6-membered saturated heterocyclic ring;

A is -N=CQ-O-, -N=CQ-NR^8-, -N=CQ-CH=N- or -N=CH-CQ=N-;

Q is 2-furyl; and

R^8 is hydrogen or (1-4C)alkyl;

provided that when R^1 and R^2 are hydrogen and A is -N=CQ-NR^8-, R^8 is not hydrogen;

or a pharmaceutically acceptable salt thereof.

It will be appreciated that depending on the nature of the substituents, in containing one or more chiral centres, the formula I compounds may exist in and be isolated in one or more different enantiomeric or racemic forms (or a mixture thereof). It is to be understood that the invention includes any of such forms which possesses the property of antagonising the actions of adenosine, it being well known how to prepare individual enantiomeric forms, for example, by synthesis from appropriate chiral starting materials or by resolution of a racemic form. Similarly, the adenosine antagonist properties of a particular form may be readily evaluated, for example by use of one or more of the standard in vitro or in vivo screening tests detailed hereinbelow.

It will also be appreciated that the first nitrogen atom in the group A, reading from left to right, is attached to the pyrimidine ring para to the group R2.

A particular value for R^1 when it is (1-6C)alkyl is, for example, methyl, ethyl, propyl or butyl, and when it is (1-4C)alkanoyl is, for example, formyl, acetyl or propionyl.

An example of a particularly preferred value for R^1 is hydrogen.

A particular value for R^3 when it is (3-12C)cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or norbornyl.

A particular value for R^3 when it is (3-6C)alkenyl is allyl.

A particular value for R^3 when it is phenyl(3-6C)alkenyl is 3-phenyl-2-trans-propenyl.

Particular values for R^3 when it is 5- or 6-membered heteroaryl include, for example, pyridyl, isoxazolyl or thiadiazolyl.

Particular values for an alkyl group when R^3 is optionally substituted (1-6C)alkyl are, for example, methyl, ethyl, isopropyl, propyl, butyl, sec-butyl and n-pentyl.

Particular values for optional substituents on alkyl when R^3 is optionally substituted alkyl (such as methyl or ethyl) include, for example:

for (3-6C)cycloalkyl: cyclopropyl;

for optionally substituted 5- or 6-membered heteroaryl:

for the 5- or 6-membered heteroaryl: furyl, pyridyl or thienyl;

for the optional substituents:

for (1-4C)alkyl: methyl;

for (1-4C)alkoxy: methoxy; and

for halogeno: fluoro, chloro or bromo;

for a group of formula $R^4(CO)_nXa(CO)_m$:

for R^4: methyl, ethyl, n-propyl, cyclohexyl, phenyl or 4-hydroxybenzyl,

for X_a: oxy, thio, NH, methylimino or,

together with R^4, piperidino.

It will be appreciated that when R^3 represents the group $R^4(CO)mXa(CO)M$, n is O when Xa is -NRb, and Rb, together with R^4 and the adjacent nitrogen atom form a 4 to 6-membered saturated heterocyclic ring.

Particular values for optional substituents on an optionally substituted 5- or 6-membered heterocyclic ring include, for example:

for alkyl: methyl or ethyl;

for alkoxy: methoxy or ethoxy; and

for halogeno: fluoro, chloro or bromo.

Particular values for optional substituents on an optionally substituted phenyl (for example where R^3 is optionally substituted phenyl or optionally substituted phenyl(1-6C)alkyl) include, for example:

for alkylenedioxy: methylenedioxy;

for halogeno: fluoro, chloro or bromo;

cyano;

trifluoromethyl;

for alkoxycarbonyl: methoxycarbonyl;
hydroxy;
hydroxymethyl;
amino;
for (1-4C)alkanoylamino:acetamido
for (1-4C)alkoxymethyl: methoxymethyl;
for alkanoyloxy: pivaloyloxy;
benzyloxy;
for halogenobenzyloxy: 4-fluorobenzyloxy or 4-chlorobenzyloxy;
for (1-4C)alkylsulphonylamino: methylsulphonylamino;
for (1-4C)haloalkylsulphonylamino: trifluoromethylsulphonylamino;
nitro;
for (1-4C)alkyl or alkoxy optionally substituted by a group of formula R^5CO:
for (1-4C)alkyl: methyl or ethyl;
for (1-4C)alkoxy: methoxy or ethoxy;
for R^5;
for (1-4C)alkoxy: methoxy, ethoxy or t-butoxy;
for (3-6C)alkylamino: n-propylamino;
for (3-6C)cycloalkylamino: cyclopentylamino or cyclohexylamino;
for (N-(1-4C)alkyl, N,N-(1-4C)dialkylamino(1-4C)alkylamino:
(N-methyl, N,N-dimethylaminoethyl)amino;
for sulphamoyl of formula $-SO_2NR^6R^7$:
for R^6 and R^7 are independently hydrogen or (1-4C)alkyl: $-SO_2NH_2$ or $-SO_2N(CH_3)_2$;
for R^6 is hydrogen and R^7 is ((2-5C)alkoxycarbonyl)$(CH_2)_q$-, carbamoyl$(CH_2)_q$- or (N-(1-4C)alkylcarbamoyl)$(CH_2)_q$: R^7 is methoxycarbonylmethyl, carbamoylmethyl or N-methylcarbamoylmethyl;
for R^6 is (1-4C)alkyl and R^7 is di(1-4C)alkylamino(1-4C)alkyl: R^6 is methyl and R^7 is dimethylaminoethyl, dimethylaminopropyl or dimethylaminobutyl.

One of the substituents on a substituted phenyl group is preferably in the para position.

A particular value for Ra when it is (1-6C)alkyl is, for example, methyl or ethyl.

Particular values for X include, for example, oxy, thio, NH, methylimino or, together with R^3, morpholino, thiomorpholino, pyrrolidino, piperidino or azetidino.

Particular values for R^8 include, for example hydrogen and methyl.

A group of compounds of particular interest consists of those compounds of formula I wherein:
R^1 is hydrogen;
R^2 is R^3X
R^3 is (1-4C)alkyl, (3-6C)alkenyl, pyridyl(1-4C)alkyl or phenyl(1-4C)alkyl optionally substituted on the phenyl moiety by 1 or 2 of halogen, hydroxy, (1-4C)alkanoyloxy, (1-4C)alkyl and (1-4C)alkoxy;
X is a direct bond, oxy, thio or NH;
A is -N=CQ-O-, -N=CQ-NR^8-, -N=CQ-CH=N- or -N=CH-CQ=N-;
Q is 2-furyl; and
R^8 is hydrogen or methyl;
and pharmaceutically acceptable salts thereof.

Of this group of compounds, those wherein R^2 is a 4-chlorobenzyl, 2-phenylethyl, 2-phenylethylamino, 2-(4-hydroxyphenyl)ethylamino, 2-(4-methylphenyl)ethylamino, 2-(4-methoxyphenyl)ethylamino or 2-(3,4-dimethoxyphenyl)ethylamino are especially preferred.

Particular pharmaceutically acceptable salts include, for example, salts with acids affording physiologically acceptable anions, for example, salts with strong acids, such as hydrochloric, hydrobromic, sulphuric, phosphoric, methanesulphonic and trifluoracetic acids. In addition, for those compounds of formula I which are sufficiently basic, suitable salts include, for example, salts with organic acids affording a physiologically acceptable anion such as salts with oxalic, citric or maleic acid. Certain compounds of formula I, for example those in which R^2 comprises a phenol group, may form base salts with bases affording physiologically acceptable cations, such as alkali metal and alkaline earth metal salts.

Specific compounds of the formula I which are of interest are described hereinafter in the accompanying examples, and the pharmaceutically acceptable acid-addition salts thereof, and these are provided as a further feature of the invention.

The compounds of formula I may be manufactured using procedures analogous to those well known in the arts of heterocyclic and organic chemistry for the production of structurally analogous compounds. Such procedures are included as a further feature of the invention and include the following preferred procedures

for the manufacture of a compound of the formula I in which R^1, R^2, X, A and Q have any of the meanings defined above:

(a) A compound of formula II in which Z^1 is a suitable leaving group, for example halogeno (such as chloro or bromo) is reacted with a compound of formula R^1NH_2.

The process is conveniently effected at a temperature in the range of, for example, from 0 to 120°C. Suitable solvents for the process include alcohols such as ethanol or isopropanol, and ethers such as tetrahydrofuran. When R^1 is hydrogen, it is particularly convenient to employ a solution of ammonia in an alcohol, such as ethanol or isopropanol, at ambient temperature.

(b) Reacting a compound of formula III or a salt thereof with a compound of formula IV or a salt thereof, in which either R^9 is a leaving group (such as (1-4C) alkoxy, for example ethoxy) and X^1 is O or NH, or $R^9$is CHO and X^1 is NH, and X^2 is O, S or NH.

The reaction may conveniently be performed in the presence of a solvent such as an alcohol (for example ethanol), a tertiary amine (for example pyridine) or a halogenated hydrocarbon, (for example chloroform). Preferably it is performed in the presence of a base, such as a tertiary amine (for example dimethylaminopyridine or pyridine). The temperature at which the reaction is performed is conveniently in the range of from 25 to 150 °C, for example from 60 to 100 °C.

When using fural-2-glyoxal as the compound of formula IV to prepare a compound of formula I in which A is -N=CH-CQ=N- or -N=CQ-CH=N-, the solvent conveniently comprises ethanol and water.

When a compound of formula I in which A is -N=CQ-CH=N- is desired, the reaction is preferably performed in the presence of an acid, for example a mineral acid such as sulphuric acid or hydrochloric acid.

(c) For the preparation of a compound of Formula I which A is -N=CQ-O- or -N=CQ-NR^8- cyclising a compound of formula V in which one of R^{10} and R^{11} is hydrogen and the other is a group of formula C(=X^4)Q in which X^3 is O or NH, and X^4 is O, S or NH.

The compound of formula V may conveniently be cyclised by treatment with a dehydrating agent, for example phosphorus pentoxide or phosphorus oxychloride. The cyclisation may be performed in the presence or absence of a solvent, conveniently at a temperature in the range of from 0 to 150 °C, for example from 50 to 120 °C.

(d) For the preparation of a compound of formula I in which A is -N=CQ-NR^8- and R^8 is (1-4C)alkyl, reacting a corresponding compound of formula I in which R^8 is hydrogen with an appropriate alkylating agent.

The alkylating agent may be a conventional alkylating agent such as a (1-4C)alkyl halide or di(1-4C)alkyl sulphate. The reaction is conveniently performed in the presence of a base, such as an alkali metal carbonate or hydroxide (for example, potassium carbonate). Suitable solvents for the reaction include amides (for example dimethylformamide), ethers (for example tetrahydrofuran) and alcohols (for example ethanol). The temperature at which the reaction is performed is conveniently in the range of from 0 to 100 °C.

(e) Reacting a compound of formula VI with an amidine of formula VII or, for a compound where R^2 is cyano, a cyanogen halide and an alkali metal cyanide.

The reaction may conveniently be performed in the presence of a solvent such as an amide (for example dimethylformamide), and at at temperature in the range of from 25 to 150 °C, for example from 60 to 120 °C. The reaction may conveniently be performed in the presence of a strong base, for example an alkali metal alkoxide such as potassium t-butoxide.

(f) For a compound of formula I in which X is O, S or NR_a, reacting a compound of formula VIII in which Z^2 is a leaving group such as a (1-4C)alkylsulphonyl group (for example methylsulphonyl) with a compound of formula R^3XH or a salt thereof.

The reaction may conveniently be performed in the presence of a solvent such as a nitrile (for example acetonitrile), an ether (for example t-butyl methyl ether, tetrahydrofuran or 1,2-dimethoxyethane) or an amide

(for example dimethylformamide), and at a temperature in the range of from 10 to 120 °C, for example from 30 to 80 °C. The reaction is preferably performed under basic conditions, which may be provided by the inherent basicity of the compound of formula R3XH or a salt thereof, or by a base such as a tertiary amine, for example pyridine or triethylamine, or an alkali metal alkoxide, for example sodium ethoxide.

It will be appreciated that those compounds in which R^1 is other than hydrogen may also be obtained by carrying out a conventional alkylation or acylation of the corresponding formula I compound in which R^1 is hydrogen obtained by one of processes (a)-(f) above.

It will also be appreciated that those compounds of formula I in which R^3 contains an acyloxy group, for example where R^3 is (1-4C)alkanoyloxyphenyl or (1-4C)alkanoyloxyphenyl(1-6C)alkyl, may be prepared by acylating the corresponding compounds of formula I in which R^3 comprises a hydroxy group, as for example where R^3 is hydroxyphenyl or hydroxyphenyl(1-4C)alkyl. The acylation may be conducted by reaction with any conventional acylating agent, for example a (1-4C)alkanoyl halide or (1-4C)alkanoic acid anhydride.

Whereafter, when a pharmaceutically acceptable salt is required, it may be obtained, for example, by reacting a compound of formula I with the appropriate acid or base affording a physiologically acceptable ion or another conventional procedure.

Similarly, when an optically active form of a chiral compound of formula I is required, either one of processes (a)-(f) above may be carried out using the appropriate optically active starting material or else a racemic form may be resolved by a conventional procedure, for example, using an optically active form of a suitable acid.

The starting materials used in the processes according to the invention are either known or may be prepared using techniques well known in the arts of heterocyclic and organic chemistry.

Thus the compounds of formula II in which Z^1 represents a halogen atom may be prepared from a compound of formula IX in which R^{12} represents a hydrogen atom or an alkoxy group (for example ethyl) and R^{13} and R^{14} are as defined for R^{10} and R^{11} above according to the method of process (c) above, but using as the dehydrating agent a reagent which is also a halogenating agent, for example phosphorus oxychloride. The reaction may be performed in the presence or absence of a solvent (such as dimethylformamide) at a temperature in the range of from 0 to 150 °C.

The compounds of formula III may be prepared by reacting a compound of formula X with a reducing agent, for example sodium dithionite, conveniently in the presence of a solvent such as aqueous ethanol. Compounds of formula III in which R^2 represents a group capable of functioning as a leaving group, for example a (1-4C)alkylthio group (such as methylthio) may also be converted into other compounds of formula III by reaction with a nucleophilic compound of formula R^3XH where X is, for example, NH. The reaction may conveniently be performed in the presence of a solvent such as water at a temperature in the range of from 40 to 120 °C.

The compounds of formula V in which one of R^{10} and R^{11} is a group of formula $C(=X^4)Q$ may be prepared by reacting a compound of formula III with a compound of formula IV in which R^9 is a leaving group such as a halogen atom (for example a chlorine atom). The reaction is conveniently performed in the presence of a solvent such as chloroform and in the presence of a base such as triethylamine. The temperature at which the reaction is performed is conveniently in the range of from 0 to 100 °C. Compounds of formula V in which R^2 represents a group capable of functioning as a leaving group, for example a (1-4C)alkylthio group (such as methylthio) may also be converted into other compounds of formula V by reaction with a nucleophilic compound of formula R^3XH where X is, for example, NH. The reaction may conveniently be performed in the presence of a solvent such as water at a temperature in the range of from 40 to 120 °C.

The compounds of formula VI may be prepared by conventional methods. For example, the compounds of formula VI in which A is -N=CQ-CH=N- may be prepared according to the method described in J. Het. Chem., 25, 1737-1740, 1988.

The compounds of formula VIII may be prepared by methods analagous to those which may be used to prepare compounds of formula I. Compounds of formula VIII in which Z^2 represents a (1-4C)alkylsulphonyl group may be prepared by reacting a compound of formula I in which R^2 represents a (1-4C)alkylthio group with an oxidising agent such as peracetic, perbenzoic or chloroperbenzoic acid. The oxidation may conveniently be performed in the presence of a solvent such as dichloromethane at a temperature in the range of from 0 to 40 °C.

The compounds of formula IX may be prepared by reacting a compound of formula VII with a compound of formula $(R^{15}OOC)CHNHCOQ$ in which R^{15} is a (1-4C)alkyl group such as ethyl, or with a compound of formula XII (preparable by reacting a compound of formula $(R^{15}OOC)CHNHCOQ$ with a dehydrating agent such as phosphorus pentoxide supported on silicon dioxide). The reaction is conveniently performed in the presence of a base, such as sodium methoxide or potassium carbonate, and a solvent such as dimethylformamide. The temperature at which the reaction is performed is conveniently in the range of from 25 to 120 °C.

The compounds of formula X may be prepared by reacting a compound of formula XI with an alkali metal

nitrite in the presence of an acid such as hydrochloric acid. The reaction is conveniently performed in the presence of a solvent such as aqueous ethanol at a temperature in the range of from 25 to 100 °C. The compounds of formula X may also be prepared by reacting a compound of formula VII with an appropriate oxime. For example, a compound in which X is O may be prepared using NCC(COOEt)=NOH as the oxime.

Certain of the starting materials used in the processes according to the invention are believed to be novel, for example the compounds of formulae II and VIII, and these are provided as further aspects of the invention.

As stated above, the compounds of formula I possess the property of antagonising one or more of the physiological actions of adenosine and are valuable in the treatment of diseases and medical conditions affecting the mammalian cardiac, peripheral and/or cerebral vascular systems, such as ischaemic heart disease, peripheral vascular disease (claudication) and cerebral ischaemia. The compounds may also be useful in the treatment of migraine.

The effects of compounds of formula I as adenosine receptor antagonists may be demonstrated in one or more of the following standard in vitro and/or in vivo tests.

(a) A_2 Adenosine receptor affinity test

This test involves the ability of a test adenosine antagonist to displace the known adenosine mimetic agent [^{3}H]-N-ethylcarboxamidoadenosine (NECA) from binding sites on membrane preparations derived from the rat phaeochromocytoma cell line PC 12 (available from the Beatson Institute, Glasgow). The basic procedure has been described by Williams et al. (J. Neurochemistry, 1987, 48(2), 498-502).

The membrane preparation is obtained as follows:
Frozen pellets of PC12 cells are washed twice with ice cold, buffered, physiological saline and the cells recovered by centrifugation (1500G) at 3°C. The separated cells are then suspended in hypotonic solution (distilled water), allowed to stand on ice for 30 minutes and are then carefully homogenized using a standard high-speed homogeniser with periodic ice-cooling to obtain a fine suspension. The homogenate is centrifuged (48000G) and the pellet is resuspended in 50 mM tris-HCl buffer, pH 7.4 containing adenosine deaminase (5 units/ml, Type VII from calf intestinal mucosa, available from Sigma Chemical Corporation, under reference no. A1280). The mixture is then incubated at 37°C. After 20 minutes, the reaction is terminated by dilution with ice-cold buffer and transfer onto ice. The material obtained containing the cell membranes is recovered by centrifugation and washed by resuspension in buffer and recentrifugation. The pellet produced is then resuspended in ice-cold buffer using a hand-driven homogenizer. The resultant membrane suspension is frozen and stored under liquid nitrogen until required.

Binding studies are carried out in microtitre plates, the assay mixtures being buffered in 50 mM tris-HCl, pH 7.4 at room temperature. The test compound is dissolved in dimethyl sulphoxide (DMSO) and then diluted with assay buffer to give the test solutions. [The final concentration of DMSO is not allowed to exceed 1% by volume, at which level it does not affect radioligand binding to the membrane receptor.] Incubations are performed at 30°C for 90 minutes in a total volume of 150 µl comprising the test solution or buffer (50 µl), tritiated NECA (50 µl) and membrane suspension (50 µl). After incubation, the samples are rapidly filtered over glass-fibre mats and the filter mats are washed to remove non-receptor-bound radioligand. Receptor-bound radioligand entrapped on the filter mats is then determined by liquid scintillation counting. Filtration and washing are carried out using a conventional vacuum filtration cell harvester. The specific binding (defined as the difference between the total binding and the non-specific binding) in the presence of the particular test compound is determined and compared with the control value. Results are conveniently expressed as the negative logarithm of the concentration required to cause a 50% displacement of control specific binding (pIC_{50}).

In general, compounds of the formula I showing antagonist activity in this assay typically show a pIC_{50} in the above test (a) of 6 or more. Thus for example, the compound of Example 1 herein showed a 78% displacement of control binding at a concentration of 10^{-5}M and 59% displacement at 10^{-7}M, indicating a pIC_{50} of greater than 7. Using the same test procedure, the known compound 1,3-dimethylxanthine typically shows a pIC_{50} of about 5.

(b) Guinea-pig Atrial Bradycardic Test

This test has also been described by Collis et al.(British J. Pharmacology, 1989, 97, 1274-1278) and involves the ability of a test compound to antagonise the bradycardic effect of the adenosine mimetic, 2-chloroadenosine, in a beating guinea-pig atrial preparation, an effect mediated via the adenosine receptor known as A_1.

The atrial pair preparation may be obtained as follows:-
Atrial pairs are obtained from guinea-pigs (Dunkin Hartley strain, 250-400g males) and mounted in organ baths

containing oxygenated Krebs buffer solution (95% O_2; 5% CO_2) at 37°C. The spontaneously beating atria are then placed under a resting tension of 1 g and allowed to equilibrate for 50 minutes with continuous overflow. Overflow is then stopped and adenosine deaminase (1 Unit\ml) added to prevent the accumulation of endogenously produced adenosine. After equilibration for 15 minutes, a cumulative dose response curve to the adenosine mimetic, 2-chloroadenosine (10^{-8}M to 10^{-4}M) is administered to produce a maximal slowing of atrial rate. After washout during 30 minutes, adenosine deaminase is readministered to the bath which is allowed to equilibrate for 15 minutes. A 10^{-5}M solution of the test compound in DMSO is then added to the bath which is left to incubate for 30 minutes. Any effect on the beating rate due to the test compound is noted before the dose response curve to 2-chloroadenosine is repeated. Compounds which are adenosine antagonists attenuate the 2-chloroadenosine response.

Test compounds are assessed by comparing dose response curves to 2-chloroadenosine alone with those obtained in the presence of the compound. Competitive adenosine antagonists produce a parallel shift in the 2-chloroadenosine dose response curve. The dose ratio (DR) is calculated from the ratio of the concentration of 2-chloroadenosine to produce a 50% reduction in atrial rate (ED_{50}) in the presence of the test compound divided by the ED_{50} concentration of 2-chloroadenosine in the absence of the test compound for each atrial pair. The pA2, which is an estimate of the concentration of antagonist required to give a dose ratio of 2, may be calculated using a standard computational technique. In this test, the known compound, 1,3-dimethylxanthine, typically shows a pA2 of about 5.

(c) Anaesthetised cat blood pressure Test

This test assesses the ability of a test compound to antagonise the fall in diastolic blood pressure produced by administration of the adenosine mimetic, 2-chloroadenosine.

Male cats (2 - 3 kg) are anaesthetised with sodium pentobarbitone (45 mg/kg, ip). The following blood vessels are catheterised: right jugular vein (for infusion of the anaesthetic at approximately 7 mg/kg per hour as a 3 mg/ml solution in isotonic saline), the left jugular vein (for administration of test agents) and the right common carotid artery (for monitoring blood pressure and pulse rate). The blood gas status and pH are determined, and are maintained within physiological limits, before administration of 2-chloroadenosine. A control dose response curve (DRC) to 2-chloroadenosine (0.3 to 30 µg/kg) against the fall in diastolic blood pressure is determined. A solution of the test compound in a mixture of 50% v/v polyethylene glycol (PEG) 400 and 0.1M sodium hydroxide is then administered i.v. and after 15 minutes the DRC to 2-chloroadenosine is determined. This procedure is repeated twice with blood gases and pH being monitored and maintained within physiological limits between each DRC. The concentration of 2-chloroadenosine required to cause a 30 mm Hg fall in diastolic blood pressure is then calculated for each dose of test compound and a Schild plot constructed for those which produce a dose ratio (DR) of >2. From this plot a K_B value is determined. Test compounds which are active in this test will possess a K_B value of 1 mg/kg (or much less).

The above Test (c) may conveniently be modified to allow evaluation of orally administered test compounds by administering the test compound to conscious cats with indwelling arterial and venous catheters and measuring the effect in preventing an adenosine induced decrease in blood pressure. Test compounds which are orally active in this test will show significant adenosine antagonist activity at a dose of 1 - 3 mg/kg or less.

(d) Anaesthetised dog Test

This test involves the assessment of the effects of a test compound on antagonising the actions of adenosine in lowering heart rate and producing vasodilation (as measured by a fall in hind-limb perfusion pressure).

Beagles (12 - 18 kg) are anaesthetised with sodium pentobarbitone (50 mg/kg, iv). The following blood vessels are catheterised: right jugular vein (for infusion of the anaesthetic at approximately 112 mg per hour as a 3 mg/ml solution in isotonic saline), right brachial vein (for administration of drugs and test agents), right brachial artery (for measurement of systemic blood pressure and pulse rate) and the left carotid artery (for administration of adenosine into the left ventricle). Both vagi, the right femoral and sciatic nerves are ligated and severed. A bolus injection of 1250 U heparin is administered before perfusing the right hindlimb at constant blood flow with blood from the iliac artery. The right leg is tied just below the ankle. Xamoterol (1 mg/kg) is then administered to the animal to stabilise heart rate at a high level and nitrobenzylthioinosine (NBTI, 0.5 mg/kg) to inhibit the uptake of adenosine. The animal is sensitised to adenosine during the equilibration time following NBTI by carrying out a dose response curve (DRC). During this time any blood gas or pH imbalance is corrected. A control DRC is performed followed by up to three DRC's after cumulative administration of the test compound (as described in (d) above). Each DRC is carried out 15 minutes after administration of test compound and after the measured parameters of heart rate and hindlimb perfusion pressure have returned

to a stable state. Similarly, blood gases and pH are maintained within physiological limits throughout the evaluation.

The amount of adenosine required to cause a 50% fall in measured parameter (ED_{50}) i.e. heart rate and hindlimb perfusion pressure is calculated for each does of test compound and a Schild plot constructed. From this plot a K_B value is determined for antagonism of heart rate response and vasodilator response to adenosine. Test compounds which are active in this test will possess a K_B value of 1 mg/kg (or much less) for vasodilator response to adenosine.

(e) Anaesthetised cat exercise hyperaemia test

This test involves assessment of the effect of a test compound to antagonise the vasodilatation response which occurs during twitch contraction of skeletal muscle. The vasodilation is mediated partly by the release of endogenous adenosine from the contracting skeletal muscle.

Cats (2.4-3.6 kg) are anaesthetised with sodium pentobarbitone (50 $mg.kg^{-1}$ ip). The following blood vessels are catheterized: left jugular vein (for infusion of anaesthetic, at approximately 0.12 $mg^{-1}min^{-1}$ as a 6 $mg.ml^{-1}$ solution in isotonic saline), right external jugular vein (for administration of drugs and test compounds), right common carotid artery (for measurement of systemic arterial blood pressure and pulse rate) and right brachial artery (for withdrawal of blood).

Blood flow to the left hind limb is measured with an electromagnetic flow probe around the left external iliac artery. The whole of the left hind limb is made to contract at 3Hz for 20 minutes duration by stimulating the sciatic and femoral nerves. Active tension produced by the extensor digitorum longus and peroneous longus muscles is measured isometrically with a force transducer. Exercise is repeated twice within the same animal, in either the absence or presence of the test compound. Test compounds are assessed for their ability to reduce the vasodilatation during skeletal muscle contraction. Test compounds which are active in this test will show significant inhibition of vasodilation during exercise at a dose of 1 mg/kg (or much less).

The compounds of the invention are generally best administered to warm-blooded animals for therapeutic or prophylactic purposes in the treatment or prevention of cardiovascular diseases and adverse conditions in the form of a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof, in a mixture or together with a pharmaceutically acceptable diluent or carrier. Such compositions are provided as a further feature of the invention.

In general, it is envisaged that a compound of formula I will be administered orally, intravenously or by some other medically acceptable route (such as by inhalation, insufflation, sub-lingual or transdermal means) so that a dose in the general range, for example, 0.001 mg to 10 (and more particularly in the range, for example, 0.05 to 5 mg/kg) mg/kg body weight is received. However, it will be understood that the precise dose administered will necessarily vary according to the nature and severity of the disease or condition being treated and on the age and sex of the patient.

A composition according to the invention may be in a variety of dosage forms. For example, it may be in the form of tablets, capsules, solutions or suspensions for oral administration; in the form of a suppository for rectal administration; in the form of a sterile solution or suspension for administration by intravenous or intramuscular injection; in the form of an aerosol or a nebuliser solution or suspension, for administration by inhalation; in the form of a powder, together with pharmaceutically acceptable inert solid diluents such as lactose, for administration by insufflation; or in the form of a skin patch for transdermal administration. The compositions may conveniently be in unit dose from containing, for example, 5 - 200 mg of the compound of formula I or an equivalent amount of a pharmaceutically acceptable salt thereof.

The compositions may be obtained by conventional procedures using pharmaceutically acceptable diluents and carriers well known in the art. Tablets and capsules for oral administration may conveniently be formed with an enteric coating (such as one based on cellulose acetate phthalate) to minimise the contact of the active ingredient of formula I with stomach acids.

The compositions of the invention may also contain one or more agents known to be of value in the diseases or conditions of the cardiovasculature intended to be treated. Thus, they may contain, in addition to the compound of formula I, for example: a known platelet aggregation inhibitor, prostanoid constrictor antagonist or synthase inhibitor (thromboxane A_2 antagonist or synthase inhibitor), cyclooxygenase inhibitor, hypolipidemic agent, anti-hypertensive agent, inotropic agent, beta-adrenergic blocker, thrombolytic agent or a vasodilator.

In addition to their use in therapeutic medicine, the compounds of formula I are also useful as pharmacological tools in the development and standardisation of test systems for the evaluation of new cardiovascular agents in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice.

The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation in vacuo;
(ii) operations were carried out at room temperature, that is in the range 18-26°C;
(iii) flash column chromatography or medium pressure liquid chromatography (MPLC) was performed on silica gel [either Fluka Kieselgel 60 (catalogue no. 60738) obtained from Fluka AG, Buchs, Switzerland, or Merck Kieselgel Art. 9385, obtained from E Merck, Darmstadt, Germany];
(iv) yields are given for illustration only and are not necessarily the maximum attainable by diligent process development;
(v) proton NMR spectra were normally determined at 200 MHz in deuterated dimethyl sulphoxide as solvent, using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d,doublet; q,quartet; and
(vi) all end-products were characterised by microanalysis, NMR and/or mass spectroscopy.

EXAMPLE 1

7-chloro-2-(2-furyl)-5-[2-(4-methoxyphenyl)ethyl]amino-oxazolo[5,4-d]pyrimidine (0.5g) and ammonium chloride (0.1g) were added to a saturated solution of ammonia in ethanol (20ml) and sealed in a Caries tube. The sealed tube was then heated at 100°C for 18 hours. The cooled reaction mixture was poured into water (200ml) and the resultant precipitate removed by filtration. The solid was recrystallised from methanol to afford **7-amino-2-(2-furyl)-5-[2-(4-methoxyphenyl)ethyl]amino**-oxazolo[5,4-d]pyrimidine (0.23g, 48.6%), m.p. 194-196°C; microanalysis, found: C, 61.5; H, 4.8; N, 19.5%; $C_{18}H_{17}N_5O_3$ requires: C, 61.5; H, 4.9; N, 19.9%; NMR (DMSO-d^6); 2.76 (t,2H ArC$\underline{H}_2$), 3.44(brq 2H, C$\underline{H}_2$NH), 3.72(s,3H,O$\underline{Me}$), 6.70(m,1H furyl-$\underline{H}$), 6.28(brs, 1H $\underline{NH}$), 6.84(d, 2H, $\underline{ArH}$), 7.13 (complex, 5H $\underline{ArH}$, N$\underline{H}_2$ furyl-H), 7.89(m,1H, furyl-$\underline{H}$); m/e $[M+H]^+$ 352.

The required starting material was prepared as follows:-

1) [(2-furanylcarbonyl)amino]propanedioic acid, diethyl ester (123g, 457mM) was added to a stirred mixture of 2-methyl-2-thio-pseudourea sulphate (63.8g, 229mM) and sodium methoxide (25% w/w) (105ml), in methanol (500ml).

The mixture was stirred at ambient temperature for 15hrs, then heated under reflux for 24 hours. Further sodium methoxide solution (260ml) was added and the mixture refluxed for a further 24 hours, cooled, poured into water and acidified with concentrated hydrochloric acid to PH<3. The mixture was then cooled to 0°C for 4 hours and the resultant precipitate separated by filtration. The solid was washed with methylene chloride, then acetone, and air-dried. Further purification was achieved by suspension in hot water for 0.5 hours. The solid was filtered off and dried at 70°C for 15 hours in a vacuum oven. This gave 4,6-dihydroxy-5-(2-furanylcarbonyl)amino-2-methylthiopyrimidine (22.5g) as a white solid (yield 18.5%) m.p. 124-125°C. NMR: NaOD; 2.66(s,3H, S$\underline{Me}$), 4.04(s,1H,$\underline{NH}$), 6.83(m,1H, furyl-$\underline{H}$), 7.39(d,1H, furyl-$\underline{H}$), 7.88(m,1H, furyl-H); m/e $[M+NH_4]^+$ 285:

2) A mixture of 4,6-dihydroxy-5-(2-furanylcarbonyl)amino-2-methylthiopyrimidine (2g, 7.5mM), p-methoxyphenethylamine (3.4g, 22.5mM), and water (25ml) was heated at 90°C for 15 hours. The mixture was then poured into water (100ml) and acidified with concentrated hydrochloric acid until PH<3. The resultant precipitate was removed by filtration and recrystallised from methanol/water (3:1) to afford 4,6-dihydroxy-5-(2-furanylcarbonyl)amino-2-[(4-methoxyphenyl)ethyl]aminopyrimidine as a white solid (0.46g, 16.6% yield) m.p. >250°C; NMR: DMSO-d^6: 2.75(t,2H,ArC$\underline{H}_2$), 3.47(brq,2H,C$\underline{H}_2$NH), 3.73 (s,3H, O$\underline{Me}$), 6.50(brs, 1H, $\underline{NH}$), 6.61(m,1H,furyl-$\underline{H}$), 6.87(d,2H,$\underline{ArH}$), 7.16(d,2H,$\underline{ArH}$), 7.17(s,1H furyl-$\underline{H}$), 7.82(d,1H,fury-$\underline{H}$), 8.64(brs,1H,$\underline{NHCO}$), 10.58(brs,2H,$\underline{OH}$ x 2); m/e $[M+H]^+$, 371:

3) A mixture of 4,6-dihydroxy-5-(2-furanylcarbonyl)amino-2-[(4-methoxyphenyl)ethyl]aminopyrimidine (408mg) and phosphorus oxychloride (5ml) was heated at 90°C for 3 hours. The excess phosphorus oxychloride was removed by evaporation, in vacuo, and then by azeotroping with toluene (2 x 50ml). The residue was added to water and the resultant precipitate filtered off, washed with water and dried. There was thus produced 7-chloro-2-(2-furyl)-5-[2-(4-methoxyphenyl)ethyl]amino oxazolo[5,4-d]pyrimidine (340mg, 83.2% yield); m.p. 169.5 - 171°C: NMR:DMSO-d^6: 2.80(t,2H,ArC$\underline{H}_2$), 3.48(q,2H, C$\underline{H}_2$NH), 3.72(s, 3H, OMe), 6.80(m,1H, furyl-$\underline{H}$), 6.85(d,2H,$\underline{ArH}$), 7.16(d,2H,$\underline{ArH}$), 7.44(d,1H,furyl-$\underline{H}$), 8.07(m, 1H, furyl-$\underline{H}$), 8.13(brs,1H,$\underline{NH}$).

EXAMPLE 2

7-Amino-5-[2-(3,4-dimethoxyphenyl)ethyl]amino-2-(2-furyl)-oxazolo[5,4-d]pyrimidine was prepared using a procedure similar to that described in Example 1, as a white solid (recrystallised from methanol/hexane); m.p. 155-158°C; microanalysis, found: C.59.4; N, 5.0; N, 18.4%; $C_{19}H_{19}N_5O_4$ requires: C, 59.8;

H,5.0; N, 18.4%; NMR (DMSO-d^6); 2.77(t, 2H, $ArCH_2$), 3.45(q, 2H, CH_2NH), 3.72(s, 3H, OMe), 3.75 (s, 3H, OMe), 6.70(complex, 5H, NH, 3 x ArH, furyl-H), 7.14(d, 1H, furyl-H), 7.18 (brs, 2H, NH_2), 7.92(m, 1H, furyl-H); m/e, $[M+H]^+$, 382:

The required starting materials were prepared as in Example 1. This gave 4,6-dihydroxy-2-[(3,4-dimethoxyphenyl)ethyl]amino-5-(2-furanylcarbonyl)pyrimidine (45.6% yield) m.p. >250°C: NMR: DMSO-d^6: 2.76(t, 2H, $ArCH_2$), 3.49(q, 2H, $NHCH_2$), 3.72(s, 3H, OMe), 3.75(s, 3H, OMe), 6.47(brs, 1H, $NHCH_2$), 6.61(m,1H, furyl-H), 6.76(d,1H,Ar-H), 6.86(m,2H, Ar-H) 7.17(d,1H, furyl-H), 7.82(brs, 1H, furyl-H), 8.64(s,1H, NHCO), 10.62(brs, 2H, 2 x OH); m/e, $[M+H]^+$, 401:

7-chloro-5-[(3,4-dimethoxyphenyl)ethyl]amino-2-(2-furyl)-oxazolo[5,4-d]pyrimidine (78% yield) m.p. 176-177°C: NMR; DMSO-d^6); 2.80(t,2H, $ArCH_2$), 3.51(q, 2H, CH_2NH), 3.71(s, 3H, OMe), 3.74(s, 3H, OMe), 6.78(complex, 4H, 3 x ArH, furyl-H), 7.43 (d,1H, furyl-H), 8.06(m, 1H, furyl-H), 8.13(brs, 1H, NH). m/e $[M+H]^+$ 401.

EXAMPLE 3

7-amino-5-(4-chlorobenzyl)-2-(2-furyl)-oxazolo[5,4-d]pyrimidine was prepared in a manner similar to that described in Example 1 except that no sealed tube was required and the reaction was carried out at ambient temperature using ammonia in isopropanol for 15 hours. The product was purified using flash column chromatography, eluting with methanol/chloroform (5/95). There was thus obtained a white solid m.p. >200°C; microanalysis, found; C, 58.8; H, 3.7%; $C_{16}H_{11}N_4O_2Cl$ requires: C, 58.8; H, 3.4%; NMR; DMSO-d^6; 4.00(s, 2H, $ArCH_2$), 6.79(m, 1H, furyl-H), 7.3%(d, 1H, furyl-H), 7.33(s, 4H, ArH), 7.75(brs, 2H, NH_2), 8.03 (d, 1H, furyl-H).

The starting material was prepared as follows:-

1) A mixture of [(2-furanylcarbonyl)amino]propanedioic acid, diethyl ester (53g, 0.2M) and acetonitrile (1 litre) was stirred at ambient temperature. Phosphorus pentoxide supported on silicon dioxide (90g) was then added slowly with brisk stirring. The mixture was heated to reflux for 2 hours and then allowed to cool over 15 hours. A further portion of phosporus pentoxide supported on silicon dioxide (85g) was added, the mixture refluxed for seven hours and then cooled over 15 hours. The mixture was filtered through diatomaceous earth and the filtrate evaporated under reduced pressure to give a yellow gum. More of this product was obtained by extraction of the filter solids with ethyl acetate, followed by evaporation of the solvent under reduced pressure.

The gum was purified by flash column chromatography, eluting with ethyl acetate/hexane (1:4). The resultant solid was recrystallised from methanol/water to give 4-carboxyethyl-5-ethoxy-2-(2-furyl)-oxazole as a solid (12.5g, 25% yield); NMR: 1.28(t, 3H, CH_3CH_2O), 1.40(t, 3H, CH_3CH_2OOC), 4.25(q, 2H, CH_3CH_2O), 4.57(q, 2H, CH_3CH_2OOC), 6.71(m, 1H, furyl-H), 7.12(d, 1H, furyl-H), 7.92(d, 1H, furyl-H).

2) A mixture of 5-carboxyethyl-4-ethoxy-2-(2-furyl)-oxazole (4.0g, 0.016M), p-chlorobenzylamidine hydrochloride (3.7g, 0.016M), anhydrous potassium carbonate (4.4g, 0.032M) and dry dimethylformamide (80ml) was heated at 100°C under argon for 3 hours. The solvent was then distilled off under reduced pressure and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was separated, dried, and concentrated to give an oil. This was purified by flash column chromatography eluting with methanol/chloroform (1:9). There was thus obtained 2-p-chlorobenzyl-4-ethoxy-5-(2-furanylcarbonyl)amino-6-hydroxypyrimidine as a pink/white solid (2.2g, 35% yield) m.p. 91.5-92.5°C; NMR; 1.20(t, 3H, CH_3CH_2O), 3.91(s, 2H, $ArCH_2$), 4.28 (q,2H, CH_3CH_2O), 6.65(m,1H, furyl-H), 7.71(d, 1H, furyl H), 7.42(s, 4H, ArH), 7.86(m, 1H, furyl-H), 9.02 (s, 1H, NHCO), 12.70(brs, 1H, OH).

3. A mixture of 2-p-chlorobenzyl-4-ethoxy-5-(2-furanylcarbonyl)amino-6-hydroxypyrimidine (2.2g, 5.9mM), dimethylaniline (1.12ml, 9mM) and phosphorus oxychloride (20ml) was heated at reflux for 2 hours. The excess phosphorous oxychloride was distilled off under reduced pressure and the residue azeotroped (x 2) with toluene. The residue was partitioned between ethyl acetate and water. The ethyl acetate extracts were dried and the solvent removed under reduced pressure. The resultant solid was further purified by flash column chromatography, eluting with hexane/ethyl acetate (65:35). There was thus obtained 7-chloro-5-(4-chlorobenzyl)-2-(2-furyl)-oxazolo[5,4-d]pyrimidine (1.2g), which was used directly without being characterised.

EXAMPLE 4

A mixture of 6-amino-8-(2-furyl)-2-[2-(4-methoxyphenyl)ethyl]amino-1H-purine (0.8g, 2.29mM), anhydrous potassium carbonate (0.347g, 2.52mM), iodomethane (157µl, 2.52mM) and dimethyl formamide (20ml) was stirred at ambient temperature under an argon atmosphere for 15 hours. The solvent was removed by distillation under reduced pressure and the residue purified by flash column chromatography eluting with me-

thanol/methylene chloride (1:20). A solid was obtained, and this was triturated with diethyl ether to afford **6-amino-8-(2-furyl)-2-[2-(4-methoxyphenyl-ethyl]amino-9-methyl-1H-purine** (0.28g) as a solid; m.p. 147-149°C; microanalysis, found: C,62.5; H, 5.3; N, 23.2%; $C_{19}H_{20}N_6O_2$ requires; C, 62.6; H, 5.5; N, 23.1%; NMR: DMSO-d^6; 2.7 - 2.85 (t, 2H, CH_2-CH_2), 3.35-3.55(q,2H,CH_2-N), 3.7-3.8(2s, 6H, OCH_3, N-CH_3), 6.2-6.35(t,1H, CH_2NH), 6.7(m,1H,furan-H), 6.7-6.8(b,2H, NH_2), 6.8-6.9(d,2H, aromatic H), 7.0(d,1H, furan-H), 7.1-7.25(d,2H, aromatic-H), 7.85(d,1H, furan-H).

EXAMPLE 5

A mixture of 2-[2-(4-methoxyphenyl)ethyl]amino-4,5,6-triaminopyrimidine (4.0g, 14.6mM), 2-(1-ethoxy-1-imino)methylfuran hydrochloride (3.84g, 21.9mM), dimethylaminopyridine (1.78g, 14.6mM) and dry pyridine (100ml) was heated at reflux, under an argon atmosphere, for two hours. The solvent was then removed by evaporation under reduced pressure and the residue purified by flash column chromatography, eluting with methanol/methylene chloride (1:25). There was thus obtained **6-amino-8-(2-furyl)-2-[2-(4-methoxyphenyl) ethyl]amino-1H-purine** as a solid (2.42g, 50% yield) m.p. 220-222°C; NMR: DMSO-d^6; 2.7-2.9(t,2H, CH_2-CH_2), 3.35-3.55(m,2H, CH_2NH), 3.7(s,3H, OCH_3), 6.1-6.2(t, 1H, NH), 6.6-6.75(m,3H, NH_2 + furan 1H), 6.8-6.9 (m,2H, aromatic-H), 7.0 (d,1H, furan-H), 7.1-7.2(m,2H, aromatic-H), 7.8(s, 1H, furan-H), 12.55 - 12.75 (b,1H, NH).

The starting material was prepared as follows:-

1) A mixture of 4,6-diamino-2-methylthio-5-nitrosopyrimidine (10g, 5.4mM), 4-methoxyphenethylamine (7.92ml, 5.4mM) and water (180ml) was heated to reflux for one hour. After cooling the red solid was separated by filtration, washed with water, and dried. There was thus obtained 4,6-diamino-2-[2-(4-methoxyphenyl)-ethyl]amino-5-nitrosopyrimidine (13.4g, 84% yield). NMR: DMSO-d^6; 2.7-2.85(m,2H, CH_2-CH_2), 3.4-3.6(m, 2H, CH_2-NH), 3.7 (s, 3H, OCH_3), 6.75-6.8(m,2H, aromatic-H), 7.05 - 7.25 (m, 2H, aromatic-H), 7.4-10.5 (m,5H, NH_2 x 2, NH), m/e $[M+H]^+$ 289.

2) A mixture of 4,6-diamino-2-[2-(4-methoxyphenyl)-ethyl]amino-5-nitrosopyrimidine (13.3g), absolute ethanol (150ml) and water (150ml) was heated almost to reflux. Sodium dithionite was added slowly, portionwise until the red colour disappeared. The mixture was filtered hot. After cooling the solid was removed by filtration, triturated with isopropyl alcohol, and dried to give 2-[2-(4-methoxyphenyl)ethyl]amino-4,5,6-triaminopyrimidine as a solid (8.2g) m.p. 134-138°C; NMR: DMSO-d^6; 2.65-2.85 (t, 2H, CH_2-CH_2), 3.25-3.5(t, 2H, CH_2-NH), 3.7 (s, 3H, OCH_3), 6.45-6.65 (b, 2H, NH_2), 6.7-6.85(b, 1H, NH), 6.8-6.9 (d, 2H, aromatic-H), 7.1-7.25(d, 2H, aromatic-H). Also 2.8 - 4.0 (v.br, 4H, 2xNH_2).

EXAMPLES 6 - 9

The following compounds of formula I were prepared by a method similar to that described in Example 4, but using the appropriate purine and methyl iodide.

EXAMPLE 6

6-Amino-8-(2-furyl)-2-[2-(4-methylphenyl)ethyl]amino-9-methyl -1H-purine; m.p. 158-160°C; NMR; DMSO-d^6; 2.2-2.3(s, 3H, CH3), 2.7-2.9 (m, 2H, CH_2-CH_2), 3.35-3.55 (m, 2H, CH_2NH), 3.8(s, 3H, NCH_3), 6.3 (t, 1H, $NHCH_2$), 6.7 (m,1H, furan -H), 6.7-6.8(b, 2H, NH_2), 7.0(d, 1H, furan-H), 7.05-7.2 (m, 4H, aromatic-H), 7.85-7.9 (d, 1H, furan-H).

EXAMPLE 7

6-Amino-8-(2-furyl)-9-methyl-1H-purine; m.p. 260 - 262°C; microanalysis, found; C, 55.7; H, 4.3; N, 31.9%; $C_{10}H_9N_5O$ requires; C, 55.8; H, 4.2; N, 32.5%; NMR: DMSO-d^6; 3.9 (s,3H, CH_3), 6.75(m,1H, furan-H), 7.2 (d, 1H, furan-H), 7.2-7.4 (b, 2H, NH_2), 7.95 (d, 1H, furan-H), 8.2 (s, 1H, N-CH-N).

EXAMPLE 8

6-Amino-2-benzylthio-8-(2-furyl)-9-methyl-1H-purine; m.p. 149-152°C; microanalysis, found; C, 59.3; H, 4.4; N, 19.9%; $C_{17}H_{15}N_5OS$, 0.5 H_2O, requires C, 59.0; H, 4.6; N, 20.2%; NMR; DMSO-d^6; 3.9 (s, 3H, N-CH_3), 4.4 (s, 2H, SCH_2), 6.7-6.8 (m, 1H, furan-H), 7.1-7.2 (d, 1H, furan-H), 7.2-7.55 (m, 7H, aromatic-H+ NH_2), 7.95 (d, 1H, furan-H).

EXAMPLE 9

6-Amino-8-(2-furyl)-9-methyl-2-methylthio-1H-purine; m.p. >250°C; microanalysis, found; C, 50.5; H, 4.1; N, 26.6%; $C_{11}H_{11}N_5OS$ requires; C, 50.6; H, 4.24; N, 26.8%; NMR; DMSO-d^6; 2.5(s, 3H, SCH_3), 3.8 - 3.9 (s, 3H, N-CH_3), 6.75(m, 1H, furan-H), 7.15 (d, 1H, furan-H), 7.3-7.5 (b, 2H, NH_2), 7.9-8.0 (d, 1H, furan-H).

EXAMPLES 10 - 14

The following compounds were prepared following the method described in Example 5, but using the appropriate triaminopyrimidine.

EXAMPLE 10

6-Amino-2-[2-(3,4-dimethoxyphenyl)ethyl]amino-8-(2-furyl)-1H-purine, m.p. 209°C (with decomposition); microanalysis, found; C, 55.9; H, 5.4; N, 20.2%; $C_{19}H_{20}N_6O_3$ (1 1/2 H_2O) requires; C, 56.0; H, 5.7; N, 20.6%; NMR; DMSO-d^6 ; 2.7 - 2.9 (t, 2H, CH_2-CH_2), 3.4-3.6(m,2H, CH_2NH), 3.7-3.8(d,6H,OCH_3 x 2), 6.6-6.7 (b, 1H, furan-H), 6.7 - 6.9 (m, 3H, aromatic-H), 7.0 (b, 1H, furan-H), 7.8-7.85(b, 1H, furan-H)>10 (NH and NH_2). m/e $[M+H]^+$ 381.

EXAMPLE 11

6-Amino-8-(2-furyl)-2-[2-(4-methylphenyl)ethyl]amino-1H-purine, m.p. 235-237°C (with decomposition); microanalysis, found; C, 59.2; H, 5.5; N, 21.4% $C_{18}H_{18}N_6O$. 0.5CH_3COOH, H_2O requires; C, 59.6; H, 5.5; N, 21.9%; NMR: DMSO-d^6 1.85(s, 1 1/2H, 1/2CH_3COOH), 2.25 (s,3H, CH_3), 2.7-2.9 (t, 2H, CH_2-CH_2), 3.4-3.55(q, 2H, $NHCH_2$), 6.1(t, 1H, NH), 6.65 (m, 2H, NH_2), 7.0 (d, 1H, furan-H), 7.05-7.2 (m, 4H, aromatic-H), 7.8 (m, 1H, furan-H).

EXAMPLE 12

6-Amino-8-(2-furyl)-2-[2-phenylethyl]amino-1H-purine, m.p. >240°C; microanalysis, found; C, 61.4; H, 4.9; N, 25.2%; $C_{17}H_{16}N_6O$ (0.6 H_2O) requires; C, 61.7; H, 5.5; N, 25.3%; NMR: DMSO-d^6 ; 2.85 (m, 2H, CH_2Ph), 3.50 (m, 2H, CH_2NH), 6.1-6.25 (b, 1H, NH), 6.55-6.75(b, 3H, NH_2 + furan-H), 6.95(d, 1H, furan-H), 7.15-7.4(m, 5H, aromatic H), 7.8(s, 1H, furan-H), 12.6 (b, 1H, NH).

EXAMPLE 13

6-Amino-2-benzylthio-8-(2-furyl)-1H-purine; m.p.234°C (with decomposition); microanalysis, found; C, 59.5; H, 4.1; N, 21.3%; $C_{16}H_{13}N_5OS$ requires; C, 59.4; H, 4.1; N, 21.7%; NMR; DMSO-d^6; 4.3-4.4 (s, 2H, CH_2-S), 6.7(m, 1H, furan H), 7.1(d, 1H, furan-H), 7.15-7.5 (m, 7H, aromatic-H+ NH_2), 7.9 (d, 1H, furan-H), 13.1-13.4 (brs, 1H, NH).

EXAMPLE 14

6-Amino-8-(2-furyl)-2-methylthio-1H-purine; m.p. >250°C; NMR; DMSO-d^6; 2.4-2.5 (s, 3H, SCH_3), 2.8-3.8 (br, 1H, NH), 6.7(d, 1H, furan-H), 7.1 (d, 1H, furan-H), 7.1-7.25 (s, 2H, NH_2), 7.8-7.9(d, 1H, furan-H).

The starting materials for Examples 10, 11, 12 were prepared as described in Example 5 starting from 4,6-diamino-2-methylthio-5-nitrosopyrimidine.

4,6-diamino-2-(2-phenylethyl)amino-5-nitrosopyrimidine; m/e $[M+H]^+$ 259;

4,6-diamino-2-[2-(3,4-dimethyoxyphenyl)ethyl]amino-5-nitrosopyrimidine m/e $[M+H]^+$ 319;

4,6-diamino-2-[2-(4-methoxyphenyl)ethyl]amino-5-nitrosopyrimidine; 2-(2-phenylethyl)amino-4,5,6-triaminopyrimidine; m/e $[M+H]^+$ 245;

2-[2-(3,4-dimethoxyphenyl)ethyl]amino-4,5,6-triaminopyrimidine; m/e $[M+H]^+$ 305; and

2-[2-(4-methylphenyl)ethyl]amino-4,5,6-triaminopyrimidine; m/e $[M+H]^+$ 258.

EXAMPLE 15

A mixture of 4-amino-5-(2-furanylcarbonyl)amino-6-hydroxy-2-(2-phenyl)ethylpyrimidine (0.4g) and phosphorus oxychloride (5ml) was heated at reflux for 30 minutes. The excess phosphorus oxychloride was re-

moved by distillation under reduced pressure followed by azeotroping with toluene (x 2). The mixture was separated between chloroform and water. The organic layer was separated, dried and the solvent distilled off under reduced pressure. The solid produced was purified by flash column chromatography eluting with methanol/methylene chloride (3:97). There was thus produced **7-amino-2 -(2-furyl)-5-(2-phenyl)ethyloxazolo[5,4-d]pyrimidine** (0.18g, 50% yield); m.p. 206-208°C; microanalysis, found: C, 66.0; H, 4.6; N, 18.2%; $C_{17}H_{14}N_4O_2$ ($0.25H_2O$) requires: C, 65.7; H, 4.7; N, 18.0%: NMR; DMSO-d^6; 2.9 - 3.15(m,4H, CH_2 x 2), 6.8(m, 1h, furan-H), 7.1-7.3 (m, 5H, aromatic-H), 7.35 (m, 1H, furan-H), 7.65-7.75 (b, 2H, NH_2), 6.0 (m, 1H, furan-H).

The starting material was prepared as follows:-

a) A mixture of sodium (0.25g, 10.8mM) and ethanol (30ml) was stirred at ambient temperature under an argon atmosphere until all the metal had dissolved. 2-Phenylethylamidine hydrochloride (1.0g, 5.43 mM) was added and the mixture stirred for 0.5 hours. Ethyl cyanoglyoxalate-2-oxime (0.77g, 5.43mM) was added and the mixture refluxed for 15 hours. After cooling, sodium ethoxide in ethanol (5.43mM) was added and the mixture refluxed for a further 2.5 hours. After cooling, the solid produced was removed by filtration. The filtrate was distilled at reduced pressure and the residue triturated with hot water. The solid residue was crystallised from methanol/methylene chloride (8:92). There was thus obtained 4-amino-6-hydroxy-5-nitroso-2-(2-phenyl)ethylpyrimidine (1.9g, 30% yield) NMR; DMSO-d^6; 2.65-2.85 (m, 2H, CH_2-CH_2), 2.85-3.1 (m,2H, CH_2-CH_2), 7.15-7.4 (m, 5H, aromatic-H), exchangeables under broad peaks.

b) A mixture of 4-amino-6-hydroxy-5-nitroso-2-(2-phenyl)ethylpyrimidine (1.1g, 4mM), ethanol (15ml) and water (35ml) was heated to approx 60°C. Sodium dithionite was added slowly, portionwise until the green colour had disappeared. The mixture was then allowed to cool, concentrated to half the original volume, and cooled again. A pale beige precipitate was formed and was removed by filtration, washed with water, and dried. There was thus produced 4,5-diamino-6-hydroxy-2-(2-phenyl)ethylpyrimidine (0.7g, 70% yield). NMR; DMSO-d^6; 2.6-2.8 (m, 2H, CH_2), 2.8-3.05(m, 2H, CH_2), 3.3-3.8 (b, 2H, NH_2), 5.5(s, 2H, NH_2), 7.1-7.4 (m,5H, aromatic-H), 11.4-11.75 (b, 1H, OH).

c) To a mixture of 4,5-diamino-6-hydroxy-2-(2-phenyl)ethylpyrimidine (0.55g, 2.39mM) and chloroform (40ml) under an argon atmosphere, was added triethylamine (365µl, 2.63mM) and then 2-furoyl chloride (258µl, 2.63mM) slowly over 0.25 hours. The mixture was stirred at ambient temperature for 15 hours. Water (50ml) was then added. The organic layer was separated, and the solvent removed by distillation under reduced pressure. There was thus produced 4-amino-5-(2-furanylcarbonyl)amino-6-hydroxy-2-(2-phenyl) ethyl pyrimidine (0.6g) as a solid; m.p. >240°C: NMR: DMSO-d^6; 2.7 (m, 2H Ar-CH_2), 2.95(m, 2H, CH_2N), 6.2 (s, 2H, NH_2), 6.6 (m, 1H, furan-H), 7.3 (m, 1H, furan-H), 7.7(m, 5H, aromatic-H), 7.8 (m, 1H, furan-H), 8.7 (s, 1H, OH), 11.7 (b, 1H, NH-CO).

EXAMPLE 16

A mixture of 7-ethoxy-5-methyl-2-(2-furyl)-oxazolo[5,4-d] pyrimidine (0.6g) and ethanol (saturated with ammonia) (20ml) in a sealed tube was heated in an autoclave at 120°C for 18 hours. After cooling, the solvent was distilled off under reduced pressure and the residue was purified by flash column chromatography, eluting with ethyl acetate/hexane (1:1), and was then further purified by flash column chromatography eluting with ammonia/methanol/methylene chloride (1:5:94). There was thus produced **7-amino-5-methyl-2-(2-furyl)-oxazolo[5,4-d]pyrimidine** (0.25g) m.p. 195-196°C; microanalysis, found; C,55.2; H, 3.6; N, 25.6%; $C_{10}H_8N_4O_2$ requires; C, 55.6; H, 3.7; N, 25.9%; NMR; DMSO-d^6; 2.4 (s, 3H, CH_3), 6.8(m, 1H, furan-H), 7.3 (d, 1H, furan-H), 7.55 - 7.75 (b, 2H, NH_2), 8.0 (m, 1H, furan -H).

The starting material was prepared as follows:-

a) A mixture of 5-carboxyethyl-4-ethoxy-2-(2-furyl)-oxazole (1.02g, 4mM) acetamidine nitrate (0.53g, 4.4mM), sodium carbonate (475mg, 4.4mM) and acetonitrile (30ml) was heated at reflux for 4 hours. After cooling the mixture was concentrated. The residual syrup was dissolved in ethyl acetate and washed with dilute sodium hydroxide (3 x 50ml). The aqueous extracts were combined, acidified with dilute hydrochloric acid and cooled. The resultant solid was filtered, washed with water and dried. There was thus produced 4-ethoxy-5-(2-furanylcarbonyl)amino-6-hydroxy-2-methylpyrimidine (0.5g, 46% yield); microanalysis, found; C, 54.8; H, 5.1; N, 15.5%; $C_{12}H_{13}N_3O_4$ requires; C, 54.8; H, 5.0; N, 16.0%.

b) A mixture of 4-ethoxy-5-(2-furanylcarbonyl)amino-6-hydroxy-2-methylpyrimidine (2.07g, 7.87mM), phosphorus oxychloride (30ml) and dimethylaniline (1.5ml, 11.7mM) was heated at reflux for one hour. After cooling, the excess phosphorus oxychloride was removed by distillation under reduced pressure. Ethanol was then added, and the mixture partitioned between methylene chloride and water. The organic layer was separated, washed with sodium bicarbonate, water, dilute hydrochloric acid, water, and dried. The solvent was then removed by distillation under reduced pressure. Ethanol (10ml) was added and the solid filtered off. This solid was further purified by flash column chromatography eluting with ethyl acetate/hex-

ane (1:3). There was thus produced 7-ethoxy-5-methyl-2-(2-furyl)-oxazolo[5,4-d]pyrimidine (1.49g, 77% yield); m.p. 104-105.5°C.

EXAMPLE 17

A mixture of 5-amino-4-cyano-2-(2-furyl)oxazole (2.33g), cyanogen bromide (1.41g), potassium cyanide (0.86g), dimethylformamide (25ml) and potassium t-butoxide (1.8g) was stirred at 60°C for 3 hours. The solvent was distilled off under reduced pressure and the residue purified by flash column chromatography eluting with ethyl acetate/hexane (40:60). The resultant solid was recrystallised from ethyl acetate/hexane. There was thus obtained **7-amino-5-cyano-2-(2-furyl)-oxazolo-[5,4-d]pyrimidine** (75mg); m.p. 260-262°C; microanalysis, found; C, 52.9; H, 2.2; N, 30.6%; $C_{10}H_5N_5O_2$ requires; C, 52.9; H, 2.2; N, 30.8%.

EXAMPLE 18

A mixture of 5-amino-4-cyano-2-(2-furyl)oxazole (190mg, 1.1mM), formamidine acetate (1.1g, 11mM) and dimethylformamide (10ml) was heated at 100°C under an atmosphere of argon for twenty minutes. The solvent was removed by distillation under reduced pressure and ethanol (5ml) added to the residue. The solid was separated by filtration. There was thus obtained **7-amino-2-(2-furyl)oxazolo-[5,4-d]pyrimidine** (0.19g) m.p. >250°C; microanalysis, found; C, 53.6; H, 2.8; N, 27.6%; $C_9H_6N_4O_2$ requires; C, 53.5; H, 3.0; N, 27.7%.

EXAMPLE 19

A mixture of 2-[2-(3,4-dimethoxyphenyl)ethyl]amino-4,5,6-triaminopyrimidine (0.5g, 1.6mM), furyl-2-glyoxal (0.2g, 1.6mM), ethanol (20ml) and water (20ml) was warmed at 60°C for 0.5 hours. The solvents were removed by distillation under reduced pressure. The resultant syrup was purified by flash column chromatography eluting with methylene chloride containing slowly increasing amounts of methanol (0 - 6%). After removal of the solvent, a syrup was obtained and this was triturated with ethyl acetate and then methanol to give a solid. There was thus obtained **4-amino-2-[2-(3,4-dimethoxyphenyl)ethyl]amino-7-(2-furyl) pteridine** (0.244g) m.p. 200 - 201°C; microanalysis, found; C, 60.8; H, 5.3; N, 20.6; $C_{20}H_{20}N_6O_3$ + 0.25 H_2O requires; C, 60.45; H, 5.2; N, 21.0%: NMR; DMSO-d^6; 2.75-2.9 (t, 2H, CH_2-CH_2), 3.5- 3.7 (q, 2H, CH_2-NH), 3.7-3.8 (d, 6H, OCH_3 x 2), 6.7-6.95(m, 4H, aromatic-H (x 3)+ furan-H), 6.95 - 7.1 (b, 1H, NH), 7.35 - 7.65 (m,3H, NH_2 + furan H), 8.0 (d, 1H, furan-H), 8.65 (s, 1H, pteridine-H); m/e $[M+H]^+$ 393.

EXAMPLES 20 - 22

The following compounds were prepared by a method similar to that described in Example 19, but using the appropriate triaminopyrimidine :-

EXAMPLE 20

4-amino-2-[2-(4-methoxyphenyl)ethyl]amino-7-(2-furyl)pteridine; m.p. 210 - 214°C (with decomposition); NMR; DMSO-d^6; 2.75 - 2.95 (t, 2H, CH_2-CH_2), 3.45 - 3.65(q, 2H, CH_2NH), 3.7 (s, 3H, OCH_3), 6.7 (m, 1H, furan-H), 6.8 - 6.9 (d, 2H, aromatic-H), 7.0 - 7.1 (b, 1H, NH), 7.1 - 7.2 (d, 2H, aromatic-H), 7.35 - 7.5 (b, 1H, furan-H), 7.5 - 7.65 (b, 2H, NH_2), 8.0 (s, 1H, furan-H), 8.65 (s, 1H, pteridine-H). m/e $[M+H]^+$ 363.

EXAMPLE 21

4-Amino-2-[2-(4-methylphenyl)ethyl]amino-7-(2-furyl)pteridine; m.p. 153-154°C; NMR; DMSO-d^6; 2.3(s,3H, CH_3), 2.85-2.95(t, 2H, CH_2-CH_2), 3.65-3.75(t, 2H, CH_2NH), 6.75(m, 1H, furan H), 7.1-7.25(q, 4H, aromatic-H), 7.5 (d, 1H, furan-H), 7.8-8.2 (b, 3H, NH_2+ furan-H), 8.8 (s,1H, pteridine-H); m/e $[M+H]^+$ 347.

EXAMPLE 22

4-Amino-2-methylthio-7-(2-furyl)pteridine. m.p. >250°C; NMR; DMSO-d^6; 2.55 (s,3H, SCH_3), 6.8(m, 1H, furan-H), 7.6 (d, 1H, furan-H), 8.05 (m, 1H, furan-H), 8.1-8.25 (b, 2H, NH_2), 9.0 (s, 1H, pteridine-H); m/e $[M+H]^+$ 260.

EXAMPLE 23

A mixture of 2-[2-(3,4-dimethoxyphenyl)ethyl]amino-4,5,6-triaminopyrimidine (1.0g, 3.2 mM), furyl-2-glyoxol (0.4g, 3.2mM), ethanol (30ml) and 2M sulphuric acid (30ml) was heated at 60°C for 1.5 hours. After cooling the solution was adjusted to PH 14 using dilute sodium hydroxide solution. The mixture was then extracted with ethyl acetate. The organic extracts were combined, dried, the solvent evaporated under reduced pressure. The resultant solid was triturated with methanol. There was thus produced **4-amino-2-[2-(3,4-dimethoxyphenyl)ethyl]amino-6-(2-furyl)-pteridine** (0.85g) m.p. 178-180°C; microanalysis, found; C, 59.1; H, 4.9; N, 20.7%; $C_{20}H_{20}N_6O_3$ + 0.75 H_2O requires; C, 59.1; H, 5.17; N, 20.7; NMR; DMSO-d^6; 2.75 - 2.9 (t, 2H, CH_2-CH_2), 3.5-3.7 (b, 2H, CH_2-NH), 3.7 - 3.8 (d, 6H, OCH_3 x 2), 6.7 (m, 1H, furan-H), 6.7- 6.9 (m, 3H, aromatic-H), 7.1 (b, 1H, NH), 7.3 (d, 1H, furan-H), 7.5 - 7.7 (b, 2H, NH_2), 7.85 (d, 1H, furan -H), 9.05 (s, 1H, pteridine-H); m/e $[M+H]^+$ 393.

EXAMPLES 24 - 26

The following compounds were prepared by a method similar to that described in Example 23 but using the appropriate triaminopyrimidine:-

EXAMPLE 24

Preparation worked up without basification. There was thus produced **4-amino-2-[2-(4-methylphenyl)ethyl]amino-6-(2-furyl)pteridine** m.p. 246-248°C (with decomposition); microanalysis; found; C, 46.2; H, 4.0; N, 16.4; S, 9.8%; $C_{19}H_{18}N_6O$+ 1.5H_2SO_4 requires; C, 46.2; H, 4.3; N, 17.0; S, 9.8%; NMR: DMSO-d^6; 2.3(s,3H, CH_3), 2.8 - 2.95(m, 2H, CH_2 - CH_2), 3.6-3.8 (b, 2H, CH_2NH), 6.8 (m, 1H, furan-H), 7.05- 7.25(m, 4H, aromatic-H), 7.5 (d, 1H, furan-H), 7.9-8.0 (b, 1H, furan-H) , 8.8 - 9.0 (b, 1H, NH), 9.2 (b, 1H, pteridine-H), 9.25 - 9.6 (b, 2H, NH_2). m/e $[M+H]^+$ 347.

EXAMPLE 25

4-Amino-2-[2-(4-methoxyphenyl)ethyl]amino-6-(2-furyl)pteridine; m.p. 212-214°C; NMR: DMSO-d^6; 2.75-2.9 (t, 2H, CH_2-CH_2), 3.45-3.6 (q, 2H, CH_2NH), 3.7 (s, 3H, OCH_3), 6.7 (m, 1H, furan-H), 6.6-6.7 (d, 2H, aromatic-H), 7.1 (b, 1H, NH), 7.15 - 7.25 (d, 2H, aromatic-H), 7.3 (d, 1H, furan-H), 7.5 - 7.7 (b, 2H, NH_2), 7.85 (m, 1H, furan-H), 9.05 (s, 1H, pteridine-H). m/e $[M+H]^+$ 363.

EXAMPLE 26

4-Amino-2-methylthio-6-(2-furyl)-pteridine; m.p. 200°C; microanalysis; found; C, 49.5; H, 3.6; N, 25.7%; $C_{11}H_9N_5O$ S (0.5H_2O) requires; C, 49.3; H, 3.7; N, 26.1%; NMR: DMSO-d^6; 2.55 (s, 3H, SCH_3), 6.75 (m, 1H, furan-H), 7.5 (d, 1H, furan-H), 7.95 (d, 1H, furan-H) 8.1-8.4 (b, 2H, NH_2), 9.3 (s, 1H, pteridine-H).

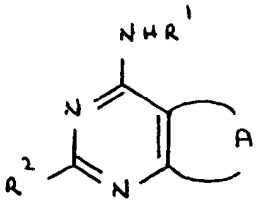
EXAMPLE 27

The following illustrate representative pharmaceutical dosage forms containing a compound of formula I, for example as illustrated in any of the previous Examples, (hereafter referred to as "compound X"), for therapeutic or prophylactic use in humans:-

(a) **Tablet**	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0
(b) **Capsule**	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CHEMICAL FORMULAE



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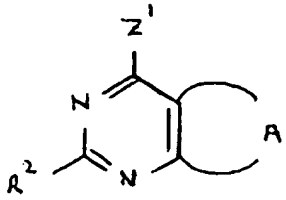

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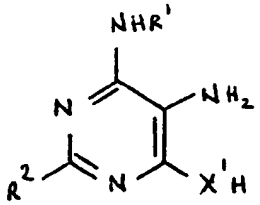

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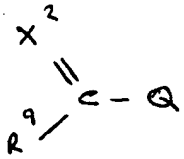

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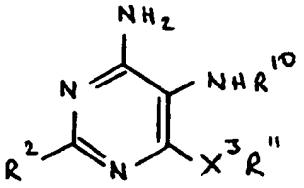

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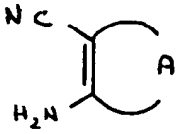
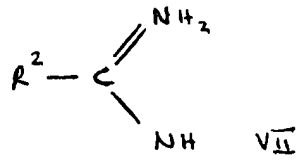


VI

CHEMICAL FORMULAE

(continued)



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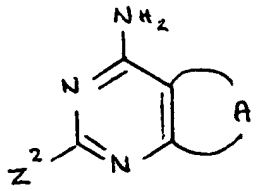

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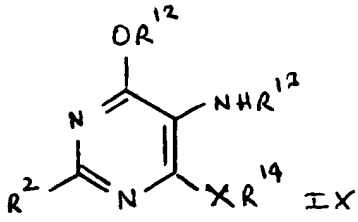
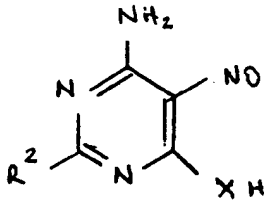


IX



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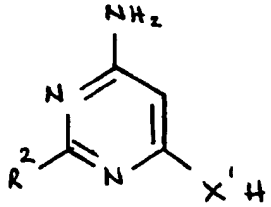

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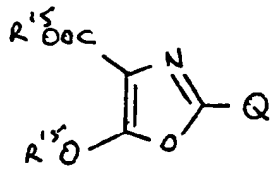


XII

Claims

1. A compound of the formula I (set out hereinafter in the final part of these claims) wherein:

R^1 is hydrogen, (1-6C)alkyl, or (1-4C)alkanoyl;
R^2 is hydrogen, cyano or a group of formula R^3X;
R^3 (when not as hereinbelow defined together with X) is (3-12C)cycloalkyl, (3-6C)alkenyl, phenyl(3-6C)alkenyl, 5- or 6-membered heteroaryl, optionally substituted (1-6C)alkyl or optionally substituted phenyl, said optionally substituted alkyl being unsubstituted or substituted by one of (3-6C)cycloalkyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted phenyl and a group of formula $R^4(CO)_nX_a(CO)_m$ in which R^4 is (1-6C)alkyl, (3-6C)cycloalkyl, optionally substituted phenyl or optionally substituted phenyl(1-4C)alkyl, n and m are each 0 or 1, provided that n+m is 0 or 1, and that when m is 0, X and X_a are separated by at least two carbon atoms, X_a is oxy, thio, sulphinyl, sulphonyl or an imino group of formula -NRb in which Rb is hydrogen, (1-6C)alkyl or together with R^4 and the adjacent nitrogen atom forms a 4 to 6-membered saturated heterocyclic ring,
said optionally substituted 5- or 6-membered heteroaryl being unsubstituted or substituted by 1 or 2 of (1-4C)alkyl, (1-4C)alkoxy and halogeno,
and any of said optionally substituted phenyl being unsubstituted or substituted by (1-4C)alkylenedioxy or by 1,2 or 3 of halogeno, cyano, trifluoromethyl, (1-4C)alkoxycarbonyl, hydroxy, hydroxymethyl, amino, (1-4C)alkanoylamino, (1-4C)alkoxymethyl, (1-4C)alkanoyloxy, benzyloxy, halogenobenzyloxy, (1-4C)alkylsulphonylamino, (1-4C)haloalkylsulphonylamino, nitro, and (1-4C)alkyl or alkoxy optionally bearing a group of formula R^5CO in which R^5 is (1-4C)alkoxy, (3-6C)alkylamino, (3-6C)cycloalkylamino or (N-(1-4C)alkyl) (N-(1-4C)dialkylamino(1-4C)alkyl)amino, and sulphamoyl of formula $-SO_2.NR^6R^7$ in which R^6 and R^7 are independently hydrogen or (1-4C)alkyl, or R^6 is hydrogen and R^7 is ((2-5C)alkoxycarbonyl)(CH2)q-, carbamoyl(CH_2)q or (N-(1-4C)alkylcarbamoyl)(CH_2)q, in which q is 0 or an integer of from 1 to 4, or R^6 is (1-4C)alkyl and R^7 is di(1-4C)alkylamino(1-4C)alkyl; and
X is a direct bond or oxy, thio, sulphinyl, sulphonyl or an imino group of formula -NRa- in which Ra is hydrogen, (1-6C)alkyl or together with R^3 and the adjacent nitrogen atom forms a 4 to 6-membered saturated heterocyclic ring;
A is -N=CQ-O-, -N=CQ-NR^8-, -N=CQ-CH=N- or -N=CH-CQ=N-;
Q is 2-furyl; and
R^8 is hydrogen or (1-4C)alkyl;
provided that when R^1 and R^2 are hydrogen and A is -N=CQ-NR^8-, R^8 is not hydrogen; or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, in which R^1 is hydrogen.

3. A compound as claimed in claim 1, in which said 5- or 6-membered heteroaryl represented by R^3 is selected from pyridyl, isoxazolyl and thiadiazolyl, and the 5- or 6-membered heteroaryl in said optionally substituted 5- or 6-membered heteroaryl is selected from furyl, pyridyl and thienyl.

4. A compound as claimed in claim 1 or claim 2, in which R^2 is hydrogen, cyano or R^3X in which R^3 is (1-4C)alkyl, (3-6C)alkenyl, pyridyl(1-4C)alkyl or phenyl(1-4C)alkyl optionally substituted on the phenyl moiety by 1 or 2 of halogen, hydroxy, (1-4C)alkanoyloxy, (1-4C)alkyl and (1-4C)alkoxy; and X is a direct bond, oxy, thio or NH.

5. A compound as claimed in claim 4, in which R^2 is 4-chlorobenzyl, 2-phenylethyl, 2-phenylethylamino, 2-(4-hydroxyphenyl)ethylamino, 2-(4-methylphenyl)ethylamino, 2-(4-methoxyphenyl)ethylamino or 2-(3,4-dimethoxyphenyl)ethylamino.

6. A compound as claimed in any one of claims 1 to 5, in which R^8 is hydrogen or methyl.

7. A compound as claimed in claim 1, in which
R^1 is hydrogen;
R^2 is R^3X
R^3 is (1-4C)alkyl, (3-6C)alkenyl, pyridyl(1-4C)alkyl or phenyl(1-4C)alkyl optionally substituted on the phenyl moiety by 1 or 2 of halogen, hydroxy, (1-4C)alkanoyloxy, (1-4C)alkyl and (1-4C)alkoxy;
X is a direct bond, oxy, thio or NH;
A is -N=CQ-O-, -N=CQ-NR^8-, -N=CQ-CH=N- or -N=CH-CQ=N-;
Q is 2-furyl; and
R^8 is hydrogen or methyl.

8. A process for the preparation of a compound as defined in claim 1, which comprises

(a) reacting a compound of formula II in which Z1 is a suitable leaving group with a compound of formula R^1NH_2,

(b) reacting a compound of formula III or a salt thereof with a compound of formula IV or a salt thereof, in which either R^9 is a leaving group and X^1 is O or NH, or R^9 is CHO and X^1 is NH, and X^2 is O, S or NH,

(c) for a compound of Formula I which A is -N=CQ-O- or -N=CQ-NR^8- cyclising a compound of formula V in which one of R^{10} and R^{11} is hydrogen and the other is a group of formula C(=X^4)Q in which X^3 is O or NH, and X^4 is O, S or NH,

(d) for a compound of formula I in which A is -N=CQ-NR^8- and R^8 is (1-4C)alkyl, reacting a corresponding compound of formula I in which R^8 is hydrogen with an appropriate alkylating agent,

(e) reacting a compound of formula VI with an amidine of formula VII or, for a compound where R^2 is cyano, a cyanogen halide and an alkali metal cyanide, or

(f) for a compound of formula I in which X is O, S or NR_a, reacting a compound of formula VIII in which Z^2 is a leaving group with a compound of formula R^3XH or a salt thereof,

whereafter, when a compound of formula I in which R^1 is (1-6C)alkyl or (1-4C)alkanoyl is desired, if necessary alkylating or acylating a corresponding compound of formula I in which R^1 is hydrogen;

when a pharmaceutically acceptable salt is required, obtaining it by reacting a compound of formula I with the appropriate acid or base affording a physiologically acceptable ion or by any other conventional procedure; and

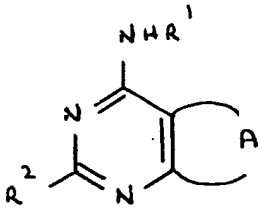
when an optically active form of a chiral compound of formula I is required, either carrying out one of processes (a) to (f) above using the appropriate optically active starting material or else resolving a racemic form by a conventional procedure; and

wherein in which R^1, R^2, X, A and Q have any of the meanings given in claim 1.

9. A pharmaceutical composition, which comprises a compound of formula I or a pharmaceutically acceptable salt thereof as defined in claim 1, in a mixture or together with a pharmaceutically acceptable diluent or carrier.

10. A compound of the formula II or VIII in which R2 and A have any of the meanings given in claim 1, Z^1 is chloro or bromo and Z^2 is (1-4C)alkylsulphonyl.

CHEMICAL FORMULAE



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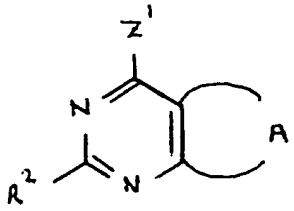

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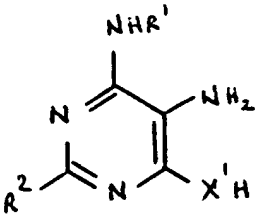

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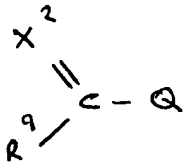

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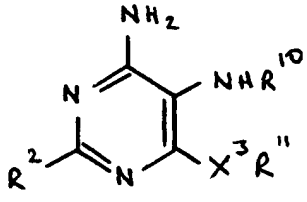

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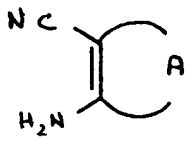

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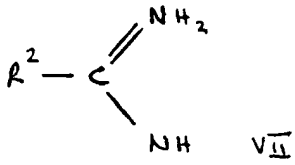

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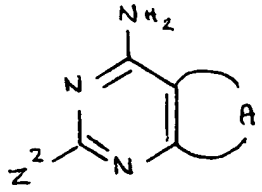

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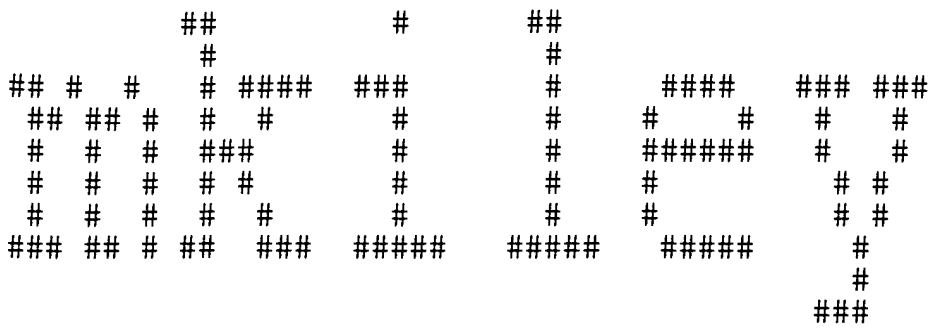

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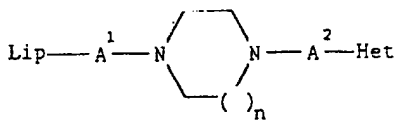
(54) Piperazine and homopiperazine derivatives, pharmaceutical compositions containing them and process for preparing the same.

(57) The lipid peroxidation inhibiting piperazine and homopiperazine derivatives of the general formula (I) and the pharmaceutically acceptable acid addition salts thereof,



(I)

Lip stands for hydrogen ; C_{15-20} alkyl ; C_{10-20} alkanoyl or C_{10-20} alkenoyl ; trityl optionally substituted by halogen ; adamantyl ; 1- or 2-naphthyloxy or oxo-substituted tetrahydronaphthyloxy ; or an amine protective group commonly used e.g. in the peptide chemistry ;

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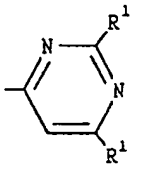
A^1 and A^2 are selected independently from the group consisting of a single bond and C_{2-3} alkylene optionally substituted by hydroxy or oxo ;

n is 1 or 2 ; and

Het represents

a group of the general formula (a),

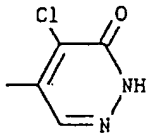


(a)

wherein

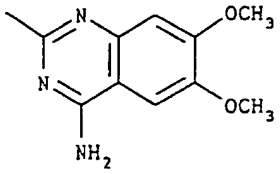
R^1 is amino or 1-pyrrolidinyl ;

or a 4-chloro-3-oxo-2,3-dihydro-5-pyridazinyl group of the formula (b) ;



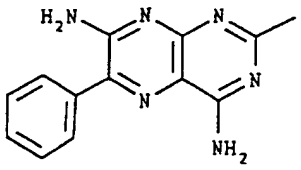
(b)

or a 4-amino-6,7-dimethoxy-2-quinazolinyl group of the formula (c) ;



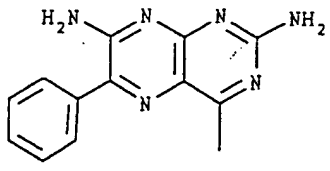
(c)

or a 4,7-diamino-6-phenyl-2-pteridinyl group of the formula (d) ;



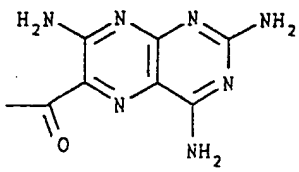
(d)

or a 2,7-diamino-6-phenyl-4-pteridinyl group of the formula (e) ;



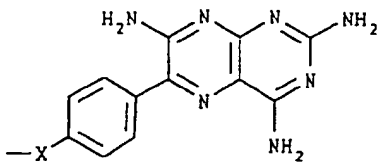
(e)

or a 2,4,7-triamino-6-pteridinylcarbonyl group of the formula (f) ;



(f)

or a group of the general formula (g);



(g)

wherein

X means oxygen, sulfur or nitrogen optionally substituted by lower alkyl,

with the first proviso that

when Het stands for a group of the general formula (a) and both A^1 and A^2 mean single bonds then Lip may not be hydrogen;

with the second proviso that

when Lip is different from naphthyloxy or oxo-substituted tetrahydronaphthyloxy then A^1 means a single bond;

with the third proviso that

when Lip represents naphthyloxy or oxo-substituted tetrahydronaphthyloxy then A^1 may not be a single bond,

as well as with the fourth proviso that

A^1 and A^2 cannot simultaneously stand for C_{2-3} alkylene optionally substituted by hydroxy or oxo.

The present invention relates to novel piperazine and homopiperazine derivatives possessing lipid peroxidation inhibitory activity, pharmaceutical compositions containing these compounds and process for their preparation.

It is known that the peroxidation of lipids in the living organism is a metal ion catalysed radical process playing an important role in a number of pathological conditions and diseases as well as in ageing. Such diseases and conditions related to the peroxidation of lipids are e.g. the injury of the brain and spinal cord, stroke, certain types of cerebrovascular spasms, tissue damages arising from ischemia (especially the so-called reperfusion injuries occuring during and after restoration of blood flow), furthermore myocardial infarction, atherosclerosis, inflammatory diseases, e.g. rheumatoid arthritis, various autoimmune diseases, drug toxicity, asthma and the like [see e.g. B. Halliwell, FASEB J. 1, 358 (1987) and J.M.C. Gutteridge and B. Halliwell, Methods in Enzymology 186, 1 (1990)].

An intensive research is being carried out worldwide to find on one hand substances which inhibit generally the oxidation processes in the living organism (antioxidants) while on the other hand to discover active agents specifically inhibiting the peroxidation of lipids. Compounds exerting the latter type of activity can be used in mammals, including man, for the prevention and/or treatment of diseases and conditions such as those mentioned above as being related to lipid peroxidation processes. Such drugs may have an outstanding therapeutical importance and active agents that can be used e.g. for the treatment of injuries of the central nervous system can be considered as life-saving medicaments.

Several endogenous substances inhibiting lipid peroxidation are present in the internal regulatory system of the mammalian organism, one of which is α-tocopherol, i.e. vitamin E [see e.g. M. J. Kelly in "Progress in Medicinal Chemistry" Vol. 25, p. 250, ed.: G. P. Ellis and G. B. West, Elsevier Science Publishers, 1988].

The objective of the present invention was to develop novel piperazine and homopiperazine derivatives being capable to effectively inhibit lipid peroxidation and as such, being useful for the treatment of various diseases and conditions of mammals, including man, where inhibition of lipid peroxidation is desirable.

Surprisingly, it was found that this requirement is met in an outstanding manner by certain piperazine and homopiperazine derivatives bearing a six-membered nitrogen heterocycle, e.g. a substituted pyrimidine or a similar condensed heterocycle, such as a phenylpteridine which heterocycle can be bound directly or through a lower alkylene chain to one of the piperazine (or homopiperazine) nitrogen atoms while a hydrocarbyl group such as those exemplified below (or occasionally hydrogen) can be attached to the other nitrogen of the piperazine (or homopiperazine) ring. Numerous compounds have been described in the literature which consist of the above three types of structural units, i.e. an open chain or cyclic hydrocarbyl group, a piperazine ring and a substituted nitrogen heterocycle.

Such compounds show various biological effects. One of these important classes of compounds includes molecules wherein the nitrogen heterocycle mentioned above, e.g. a pyridine or pyrimidine ring substituted by amino groups as well as the hydrocarbyl group has been varied in a wide range. Thus the hydrocarbyl group may be e.g. a steroid skeleton (published PCT applications Nos. WO 87/01706 and WO 87/07895), a secosteroid (published PCT-application No. WO 88/07527) or various substituted alkyl groups of medium chain length, various mono and bicycles, e.g. a substituted phenyl, phenoxyalkyl, benzopyranyl and the like (published PCT application WO 88/08424). These classes of compounds were claimed to possess lipid peroxidation inhibitory activity. It should be noted that no such molecules bearing an alkenyl, alkanoyl, alkenoyl or an alkyl of more than 14 carbon atoms are disclosed.

In an other large group of compounds containig the three characteristic structural elements mentioned above, various types of hydrocarbyl groups being either similar to or different from those mentioned above are present, together with the nitrogen heterocycles which latter are nearly identical to those discussed in the preceeding paragraph. Thus e.g. phenyl, benzyl and benzhydryl [French patent specification No. 1,507,062, published German patent applications Nos. 1,947,332 and 2,211,738, Belgian patent specification No. 739,283 and Canadian patent specification No. 983,497 as well as the published Japanese patent application (Kokai) No. 74/76887], benzodioxolyl and benzodioxanyl [Canadian patent specifications Nos. 979,894, 983,493, 983,494 and 983,495 ; and the published Japanese patent applications (Kokai) Nos. 74/72270, 74/72271, 74/72272 and 74/72273], further a 3-trityl-n-propylgroup [G. L. Regnier et al., J. Med. Chem 15, 295 (1972)] occur as characteristic structural elements. (It should be noted that no derivatives containing naphthyloxyalkyl, trityl or adamantyl attached to the piperazine nitrogen are mentioned among the above compounds.) A high number of the latter compounds has been described to show various biological effects (such as vasodilatory, sedative, analgetic, antiinflammatory and respiration promoting effects), an eventual lipid peroxidation inhibitory activity has, however, never been mentioned.

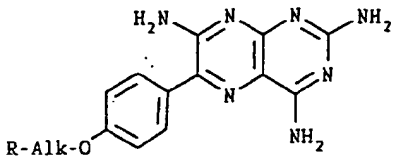
In addition to the above classes of compounds containing a piperazine ring and a further nitrogen heterocycle several other types of compounds have been published to inhibit the peroxidation of lipids. In the following some examples are given : cyclic hydroxamic acids [Y. Teshima et al., J. Antibiot. 44, 685 (1991)]; pyrimidine-

diones (published European patent application No. 447,324); acylamino-7-hydroxyindane derivatives [Y. Oshiro et al., J. Med. Chem. 34, 2014 (1991)]; amino analogues of vitamin C (published European patent applications Nos. 446,539 and 447,325); monocyclic analogues of vitamin E (Japanese patent specification No. 01,226,843); 4-arylthiopiperidine derivatives (published European patent application No. 433,167); 1,4-benzoquinones [e.g. G. Goto, et al.Chem.Pharm. Bull. 33, 4422 (1985)]; carboxyalkyl and hydroxyalkyl naphthoquinones [K. Okamoto et al., Chem. Pharm. Bull. 30, 2797 (1982)]; selenium compounds [A. Muller et al., Biochem. Pharmacol. 33, 3235 (1984) and A.L. Tappel, Fed. Proc. 24, 73 (1965)]; curcuminoids [S. Toda et al., J. Ethnopharmacology. 23, 105 (1988)]; quinazoline derivatives (published European patent application No. 302,967); pyridylquinolines (published European patent application No. 289,365); dihydroquinoline derivatives [A. Blazovics et al., Free Radical Res. Commun. 4, 409 (1988)]; anthron and acridine derivatives [P. Frank, Biochem. Biophys. Res. Commun. 140, 797 (1986)] ; dihydropyridinethiones [A. G. Odynets et al., Eksp. Med. (Riga) 21, 127 (1986); Chem. Abstr. 106, 148956]; pyrazolone derivatives (Japanese patent specification No. 62,149,617); benzothiazines (Japanese patent specification No. 01,287,077); flavonoids (see e.g. R. Campos et al., Planta Med. 55, 417 (1989)]; pyrimidopyrimidines [I. Bellido et al., Meth. Find. Exp. Clin. Pharmacol. 13, 371 (1991)]; methylated uric acid analogues [Y. Nishida, J. Pharm. Pharmacol. 43, 885 (1991)]; methylprednisolone [see e.g. H. B. Demopoulos et al., Can. J.Physiol. Pharmacol. 60, 1415 (1982)]; dehydroalanine derivatives [P. Buc-Calderon et al., Arch. Biochem. Biophys. 273, 339 (1989)]; acylated polyamines [J. M. Braughler et al., Biochem. Pharmacol. 37, 3853 (1988)].

The literature data cited above illustrate that the compounds containing a mono or diamino substituted nitrogen heterocycle attached to a piperazine ring do not necessarily inhibit lipid peroxidation and, on the other hand, the presence of the above nitrogen heterocycles is not imperative for the same biological activity.

As referred to above the desired lipid peroxidation inhibitory activity is shown also by certain novel piperazine derivatives wherein a phenylpteridine ringsystem is attached, optionally-through an alkylene chain to one of the nitrogen atoms in a piperazine ring ; in the most preferable compounds of this type the other nitrogen is unsubstituted.

The Belgian patent specification No. 901,850 and the published German patent application No. 2,700,073 disclose compounds of the general formula (A)

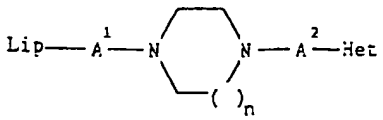


(A)

wherein R stands for a substituted amino and Alk means an optionally substituted alkylene chain. In these compounds R may be e.g. mono or dialkylamino, benzylamino or a five or six-membered heterocyclic group optionally containing one or two additional heteroatoms such as morpholinyl, piperidinyl, pyrrolidinyl or 4-methyl-1-piperazinyl. These patent specifications do not describe compounds containing piperazinyl groups being unsubstituted or substituted with a group other than methyl in position 4 as R. It has been published in the above two patent specifications as well as in papers [see e.g. H. Priewer et al., Arzneim.-Forsch./Drug Res. 35, 1819 (1985); Pharm. Res. 3, 102 (1986); Drugs of the Future 11, 669 (1986)] that the above compounds possess diuretic, potassium retaining, calcium antagonist and cardioprotective activities, but an eventual lipid peroxidation inhibitory activity was not mentioned.

In the lipid peroxidation inhibitory novel piperazine and homopiperazine derivatives of the present invention a six-membered, optionally substituted heterocycle containing two nitrogen atoms and being optionally condensed with a benzene or pyrazine ring (such as a pyrimidine, pyridazine, quinazoline or pteridine) is attached, optionally through an alkylene chain, to one of the nitrogen atoms in a piperazine (or homopiperazine) ring, while a long, open-chain hydrocarbyl group, a moiety containing two, optionally partially saturated condensed carbocycles (e.g. naphthyl) connected via an oxygen atom and a lower alkylene chain, a methyl group bearing three noncondensed unsaturated carbocycles (e.g. trityl) or a moiety consisting of three condensed saturated carbocycles (adamantyl) may be bound to the other nitrogen atom in the piperazine (or homopiperazine) ring; or the latter nitrogen may also be unsubstituted.

Accordingly, the present invention provides compounds of the general formula (I)



(I)

wherein

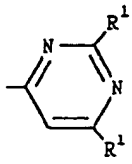
Lip stands for hydrogen; C_{15-20} alkyl; C_{10-20} alkanoyl or C_{10-20} alkenoyl; trityl optionally substituted by halogen; adamantyl; 1- or 2-naphthyloxy or oxo-substituted tetrahydronaphthyloxy; or an amine protective group commonly used e.g. in the peptide chemistry;

A^1 and A^2 are selected independently from the group consisting of a single bond and C_{2-3} alkylene optionally substituted by hydroxy or oxo;

n is 1 or 2; and

Het represents

a group of the general formula (a),

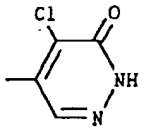


(a)

wherein

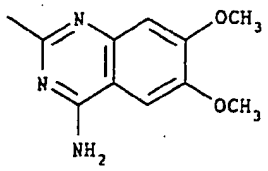
R^1 is amino or 1-pyrrolidinyl;

or a 4-chloro-3-oxo-2,3-dihydro-5-pyridazinyl group of the formula (b);



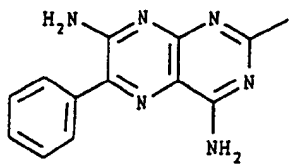
(b)

or a 4-amino-6,7-dimethoxy-2-quinazolinyl group of the formula (c);



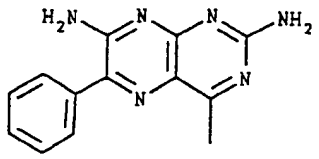
(c)

or a 4,7-diamino-6-phenyl-2-pteridinyl group of the formula (d);



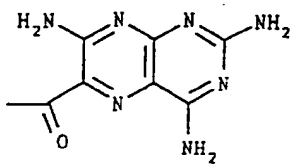
(d)

or a 2,7-diamino-6-phenyl-4-pteridinyl group of the formula (e);



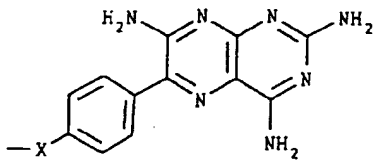
(e)

or a 2,4,7-triamino-6-pteridinylcarbonyl group of the formula (f);



(f)

or a group of the general formula (g);



(g)

wherein

X means oxygen, sulfur or nitrogen optionally substituted by lower alkyl,

with the first proviso that

when Het stands for a group of the general formula (a) and both A^1 and A^2 mean single bonds then Lip may not be hydrogen;

with the second proviso that

when Lip is different from naphthyloxy or oxo-substituted tetrahydronaphthyloxy then A^1 means a single bond;

with the third proviso that

when Lip represents naphthyloxy or oxo-substituted tetrahydronaphthyloxy then A^1 may not be a single bond, as well as with the fourth proviso that

A^1 and A^2 cannot simultaneously stand for C_{2-3} alkylene optionally substituted by hydroxy or oxo,

as well as their pharmaceutically acceptable acid addition salts and pharmaceutical compositions containing these compounds.

According to another aspect of the invention, there is provided a process for the preparation of the novel

compounds of the general formula (I) and the pharmaceutically acceptable salts thereof.

Due to their lipid peroxidation inhibitory effect, preferred are the compounds of the general formula (I), wherein

Lip means an open-chain or cyclic lipophilic group, e.g. a C_{10-20} alkenoyl, o-chlorotrityl, 1- or 2-naphthyloxy;

A^1 represents a single bond, 2-hydroxy-1,3-propylene or CH_2CO;

A^2 is a single bond;

n is 1 or 2; and

Het means a group of the general formula (a).

Similarly, by virtue of their lipid peroxidation inhibitory effect, preferred are the compounds of the general formula (I), wherein

Lip means hydrogen;

A^1 is a single bond;

A^2 represents 1,3-propylene optionally substituted by hydroxy;

or ethylene optionally substituted by oxo;

n is 1 or 2; and

Het stands for a group of the general formula (g),

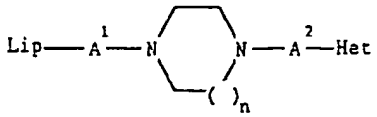
wherein

X is as defined above.

Certain compounds of the general formula (I), wherein Lip means an amine protective group being commonly used in peptide chemistry, are also advantageous since they are useful intermediates in the synthesis of other compounds of the general formula (I).

The pharmaceutically acceptable acid addition salts of the compounds of the general formula (I) are salts formed with the usual known, non-toxic organic or inorganic acids, such salts include the hydrochlorides, sulfates, phosphates, tartrates, fumarates, citrates and the like.

The compounds of the present invention can be prepared by using various methods known per se. These methods differ from each other in the order of coupling of the individual structural elements of the compounds of the invention, i.e. Lip, the piperazine (or homopiperazine) ring and Het. Thus, according to the invention, the compounds of the general formula (I),



(I)

wherein Lip, A^1, n, A^2 and Het are as defined above and their pharmaceutically acceptable acid addition salts can be prepared by the following methods :

a) for preparing compounds of the general formula (I), wherein

Lip is as defined in the introduction, with the proviso that it may not be hydrogen or an amine protective group;

A^1 is as defined in the introduction, with the proviso that when Lip stands for naphthyloxy or oxo-substituted tetrahydronaphthyloxy then it may not be a single bond; and

n, A^2 and Het are as defined in the introduction,

a compound of the general formula (II),

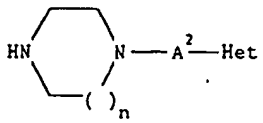
$$Lip\text{-}A^1\text{-}L^1 \quad (II)$$

wherein

Lip and A^1 are as defined above and

L^1 is a leaving group,

is reacted with a compound of the general formula (III),



(III)

wherein

n, A^2 and Het are as defined above; or

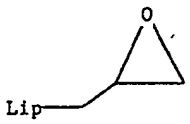
b) for preparing compounds of the general formula (I), wherein

Lip means naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

A^1 stands for 1,3-propylene substituted by hydroxy; and

n, A^2 and Het are as defined in the introduction,

a compound of the general formula (IV),

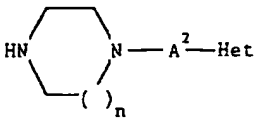


(IV)

wherein

Lip is as defined above,

is reacted with a compound of the general formula (III),



(III)

wherein

n, A^2 and Het are as defined above; or

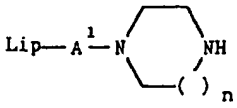
c) for preparing compounds of the general formula (I), wherein

Lip is as defined in the introduction, with the proviso that it may not be hydrogen;

A^1 is as defined in the introduction, with the proviso that when Lip stands for naphthyloxy or oxo-substituted tetrahydronaphthyloxy then A^1 may not be a single bond; and with the other proviso that when Lip stands for an amine protective group then A^1 is a single bond; and

n, A^2 and Het are as defined in the introduction,

a compound of the general formula (V),



(V)

wherein

Lip, A^1 and n are as defined above,

is reacted with a compound of the general formula (VI),

L^2-A^2-Het

(VI)

wherein

A^2 and Het are as defined above, and

L^2 stands for a leaving group; or

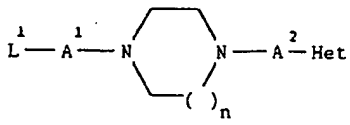
d) for preparing compounds of the general formula (I), wherein

Lip means naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

A^1 is as defined in the introduction, with the proviso that it may not be a single bond; and

n, A^2 and Het are as defined for formula (I),

a compound of the general formula (VII),



(VII)

wherein

A^1, n, A^2 and Het are as defined above, and

L^1 stands for a leaving group,

is reacted with a compound of the general formula Lip-H,

wherein

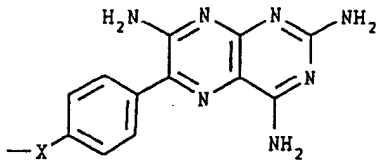
Lip is as defined above; or

e) for preparing compounds of the general formula (I), wherein

Lip is as defined in the introduction, with the proviso that it may not be naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

A^1 is a single bond;

Het stands for a group of the general formula (g),



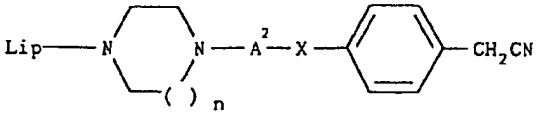
(g)

wherein

X is as defined in the introduction; and

n and A^2 are as defined above,

a compound of the general formula (VIII),



(VIII)

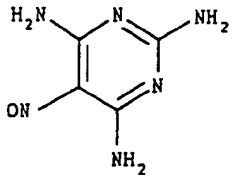
wherein

Lip is as defined above, with the proviso that it may not be hydrogen, naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

X means oxygen, sulfur or nitrogen optionally substituted by lower alkyl; and

n and A^2 are as defined above,

is reacted with 5-nitroso-2,4,6-triaminopyrimidine of the formula (IX),



(IX)

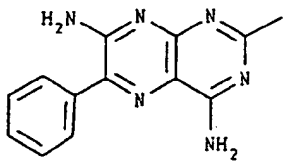
and in the case when Lip stands for an amine protective group, this protective group is removed from the compound thus obtained; or

f) for preparing compounds of the general formula (I), wherein

Lip is as defined in the introduction, with the proviso that it may not be naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

both A^1 and A^2 are single bonds;

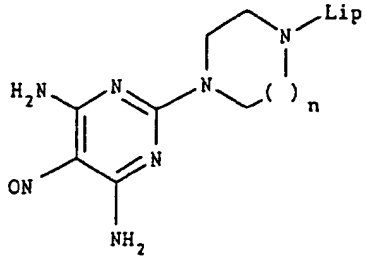
Het stands for a group of the formula (d);



(d)

and n is as defined in the introduction,

a compound of the general formula (X),



(X)

wherein

Lip is as defined above, with the proviso that it may not be hydrogen, naphthyloxy or oxo-substituted tetrahydronaphthyloxy; and

n is as defined above,

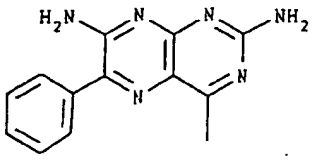
is reacted with benzyl cyanide and in the case when Lip stands for an amine protective group, this protective group is removed from the product thus obtained; or

g) for preparing compounds of the general formula (I), wherein

Lip is as defined in the introduction, with the proviso that it may not be naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

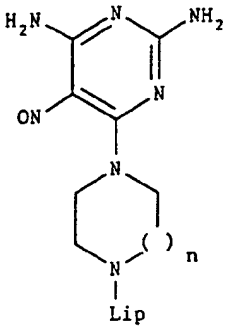
both A^1 and A^2 are single bonds;

Het stands for a group of the formula (e);



(e)

and n is as defined in the introduction,
a compound of the general formula (XI),



(XI)

wherein

Lip is as defined above, with the proviso that it may not be hydrogen, naphthyloxy or oxo-substituted tetrahydronaphthyloxy; and

n is as defined above,

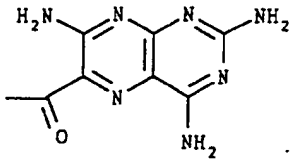
is reacted with benzyl cyanide and in the case, when Lip stands for an amine protective group, this protective group is removed from the product obtained; or

h) for preparing compounds of the general formula (I), wherein

Lip is as defined in the introduction, with the proviso that it may not be naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

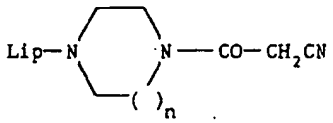
both A^1 and A^2 are single bonds;

Het stands for a group of the formula (f);



(f)

and n is as defined for formula (I),
a compound of the general formula (XII),



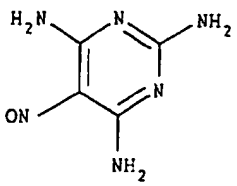
(XII)

wherein

Lip is as defined above, with the proviso that it may not be hydrogen, naphthyloxy or oxo-substituted tetrahydronaphthyloxy; and

n is as defined above,

is reacted with 5-nitroso-2,4,6-triaminopyrimidine of the formula (IX)



(IX)

and in the case, when Lip stands for an amine protective group, this protective group is removed from the product thus obtained, and, if desired, the compound of the general formula (I) prepared by any of the above processes a) - h) is converted to its acid addition salt.

The leaving groups L^1 and L^2 in the compounds of the general formulae (II), (VI) and (VII) may independently be e.g. halogen atoms such as chlorine, bromide or iodine; or sulfonyloxy groups, e.g. methanesulfonyloxy, benzenesulfonyloxy or p-toluene-sulfonyloxy.

An amine protective group as Lip in the compounds of the general formulae (V), (VIII), (X), (XI) or (XII) may be any group of this type being commonly used in the peptide chemistry; preferred protective groups are e.g. tert-butoxycarbonyl, formyl, benzyloxycarbonyl and the like.

The preferred embodiments of the above processes a) - h) will be discussed in detail hereinafter.

Process a)

The compounds of the general formula (II) are reacted with the compounds of the general formula (III) in an inert organic solvent, e.g. in a halogenated hydrocarbon such as chloroform or methylene chloride; in an alcohol such as methanol or ethanol; in an ether-like solvent such as diethyl ether or tetrahydrofuran; in acetonitrile, dimethylformamide or the like at a temperature between 0 °C and the reflux temperature of the solvent, optiohally in the presence of an inorganic base, e.g. potassium carbonate or an organic base, e.g. triethylamine or pyridine. Pyridine can also be used as solvent.

The compounds of the general formula (II) used as starting substances are commercially available or can be prepared by using methods known from the literature.

It should be noted that for preparing compounds of the general formula (I), wherein

Lip means alkanoyl or alkenoyl; and

A^1 is a single bond,

the acyl groups mentioned above may be introduced also by using carboxylic acids of the general formula (II) wherein L^1 stands for hydroxy. In such cases the reaction with the compounds of the general formula (III) is preferably carried out in the presence of a condensing agent such as carbonyldiimidazole or a carbodiimide, e.g. dicyclohexylcarbodiimide or the like.

Certain compounds of the general formula (III) are known from the literature [see e.g. the published PCT patent application No. Wo 87/01706; T. H. Althuis and H. J. Hess: J. Med. Chem. 20, 146 (1977)]; while other analogues can be prepared by using the methods illustrated by the Examples hereinbelow.

Process b)

The compounds of the general formula (IV) are reacted with the compounds of the general formula (III) in an inert solvent such as an alcohol, e.g. methanol or ethanol, at a temperature between room temperature and the reflux temperature of the solvent.

The starting substances of the general formula (IV) are known from the literature or can be prepared in an analogous way [E.Fourneau and M. Trefouel, Bull. Soc. Chim. France [4], 43, 454 (1928)].

Process c)

The compounds of the general formula (V) are reacted with the compounds of the general formula (VI) under similar conditions as described for process b) above, at a temperature between 50 °C and 200 °C.

The starting substances of the general formulae (V) and (VI) are known or can be prepared by analogy of the known compounds [see e.g. P.E. Aldrich et al., J. Med. Chem. 14, 535 (1971); B. Roth et. al., J. Am. Chem. Soc. 72, 1914 (1950); J. Mowry, J. Am. Chem. Soc. 75, 1909 (1953); the published German patent application No. 2,550,111 and the published PCT patent applications Nos. WO 87/01706 and WO 88/08424].

Process d)

The compounds of the general formula (VII) are reacted with the compounds of the general formula Lip-H in an inert organic solvent such as a polar solvent, e.g. acetonitrile or dimethylformamide; a halogenated hydrocarbon, e.g. chloroform or methylene chloride, optionally in the presence of an inorganic base, e.g. potassium carbonate or an organic base, e.g. triethylamine or pyridine, at a temperature between 0 °C and the boiling point of the solvent. Alternatively, a salt (e.g. alkali metal salt) of the compounds of the general formula Lip-H may be formed with a suitable base and reacted with the compound of the general formula (VII).

The starting substances of the general formula (VII) can conveniently be prepared by reaction of the appropriate compound of the general formula (III) with a compound of the general formula L^1-A^1-L^2, wherein

A^1 is as defined for the general formula (I) in the introduction, with the proviso that it may not be a single bond; and

L^1 and L^2 stand independently for leaving groups,

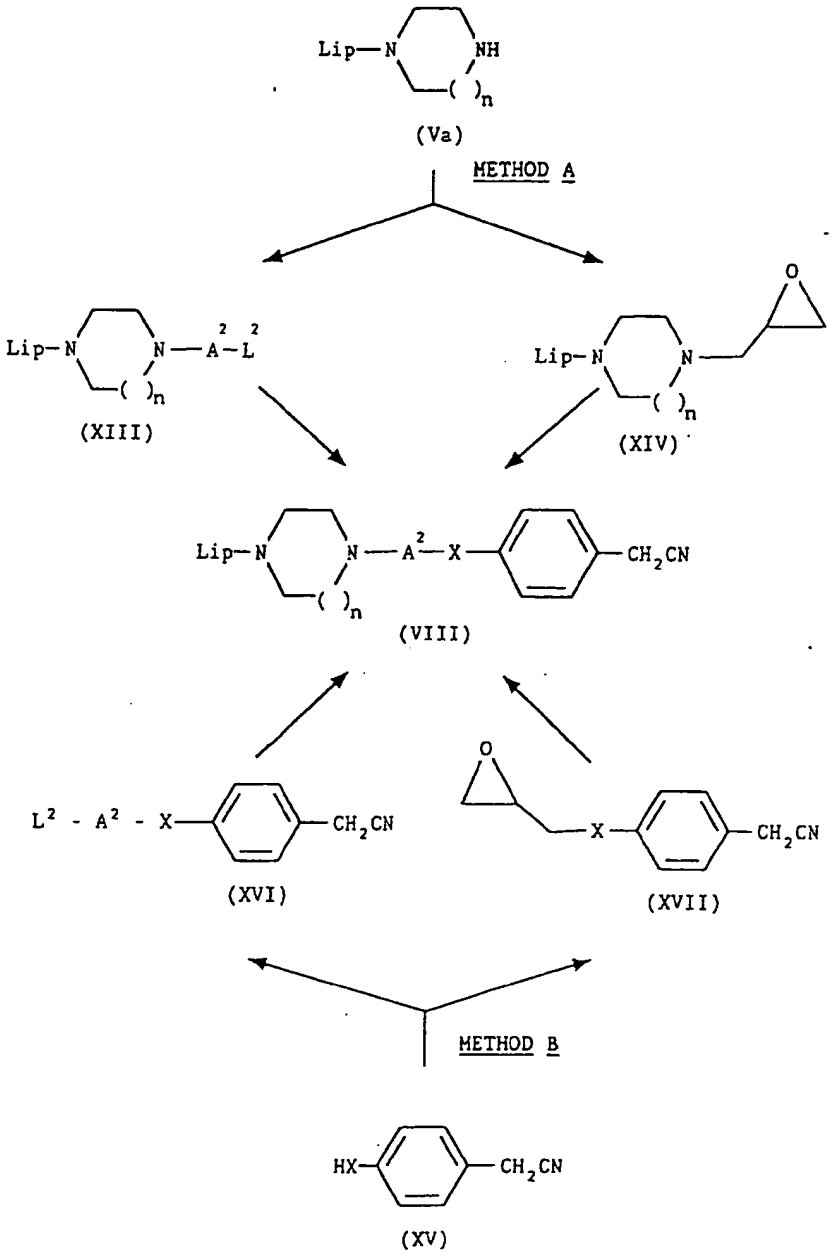
under conditions described for process a) above.

Process e)

The compounds of the general formula (VIII) are reacted with 5-nitroso-2,4,6-triaminopyrimidine of the formula (IX) under the usual conditions described in the literature for the preparation of 2,4,7-triamino-6-arylpteridines [see e.g. D. J. Brown in: "Fused Pyrimidines", pages 113-120 and 359-360 in the series "The Chemistry of Heterocyclic Compounds", Eds. E. C. Taylor and A. Weissberger, John Wiley and Sons, Interscience (1988); further the Hungarian patent specification No. 195,817] in an inert solvent, such as a substituted alcohol, e.g. 2-methoxyethanol or 2-ethoxyethanol, or dimethylformamide, N-methylpyrrolidone or the like at a temperature between room temperature and the reflux temperature of the solvent, preferably at a temperature between 100 °C and 140 °C, in the presence of a strong base, such as an alkali metal hydroxide, carbonate or alkoxide, e.g. sodium hydroxide, potassium carbonate or sodium 2-ethoxyethoxide.

When in process e) a compound of the general formula (I) containing an amine protective group as Lip is prepared, the protective group can be removed by any usual method known per se, e.g. in a separate reaction step. The method used for removing the protective group is chosen according to the nature of the protective group in question. Thus e.g. a tert-butoxycarbonyl may be removed in an aqueous or anhydrous medium by using a suitable acid, e.g. hydrochloric acid, formic acid or trifluoroacetic acid; benzyloxycarbonyl may be cleaved off e.g. by catalytic hydrogenation; whereas formyl may be removed by using e.g. a strong mineral acid, such as hydrochloric acid or a strong base such as an alkali metal hydroxide under heating. Alternatively, the compounds of the general formula (I) containing an amine protective group as Lip may be further reacted without isolation, i.e. the protective group may be removed in the same reaction mixture used for the preparation of the protected compound. In this case the unprotected final compounds of formula (I) wherein Lip is hydrogen are isolated and purified.

The starting compunds of the general formula (VIII) may be prepared e.g. by any of two methods illustrated by the following reaction scheme.



According to method A) shown in the reaction scheme, first a compound of the general formula (Va) [i.e. a compound of the general formula (V), wherein A^1 is a single bond],

wherein

Lip and n are as defined in the introduction for the general formula (I), with the proviso that Lip may not be hydrogen,

is reacted either with a compound of the general formula L^1-A^2-L^2,

wherein

A^2 is as defined for the general formula (I) in the introduction, with the proviso that it may not be a single bond, and

L^1 and L^2 are independently leaving groups,

or with epichlorohydrine e.g. under conditions described for process a) above to obtain a compound of the general formula (XIII) or (XIV)

wherein

Lip, n and A^2 are as defined for the general formula (I) in the introduction, with the proviso that A^2 may not be a single bond; and

L^2 means a leaving group.

Subsequently the compound of the general formula (XIII) or (XIV) thus obtained is reacted with a substituted benzyl cyanide of the general formula (XV)

wherein

X means oxygen, sulfur or nitrogen optionally substituted by lower alkyl,

in an inert organic solvent, optionally in the presence of a base to obtain the desired intermediate of the general formula (VIII).

Alternatively, according to method B) shown in the scheme, first a substituted benzyl cyanide of the general formula (XV), wherein X is as defined above, is reacted either with a compound of the general formula L^1-A^2-L^2, wherein L^1, L^2 and A^2 are as defined above, or with epichlorohydrine e.g. under conditions described for the above method A) in a manner known per se. Then the compound of general formula (XVI) or (XVII) thus obtained is reacted with a compound of the general formula (Va), wherein Lip and n are as defined above, to obtain the desired intermediate of the general formula (VIII).

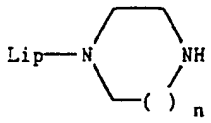
The starting substances used in the two methods described above, i.e. the compounds of the general formulae (Va) and (XV) are known or can be prepared by using known methods as described hereinafter in the Examples. The compounds of the general formula L^1-A^2-L^2 are similarly known; preferred compounds of this type are e.g. 1-bromo-3-chloropropane and 2-chloroacetyl chloride.

5-Nitroso-2,4,6-triaminopyrimidine of formula (IX) used as starting substance in the present process is also known [see e.g. H. Sato et al., J. Chem. Soc. Japan, Pure Chem. Sect. 72, 866 (1951)].

Process f)

The compounds of the general formula (X) can be reacted with benzyl cyanide e.g. by using the method described in process e) and a protective group optionally present may be removed e.g. in the same way as described therein.

The starting compounds of the general formula (X) can be prepared e.g. in such a way that first a compound of the general formula (Va),

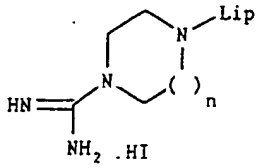


(Va)

wherein

Lip and n are as defined for the general formula (I) in the introduction, with the proviso that Lip may not be hydrogen,

is reacted with S-methylisothiuronium iodide in a manner described e.g. in the published European patent application No. 0,039,190 to obtain piperazinylamidine hydroiodide of the general formula (XVIII),

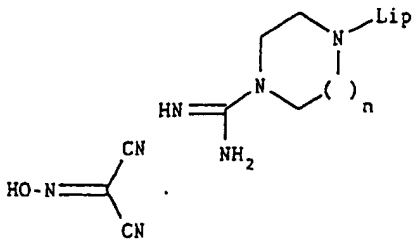


(XVIII)

wherein

Lip and n are as defined for the formula (Va).

Subsequently a salt of the general formula (XIX),



(XIX)

wherein

Lip and n are as defined for the formula (Va),

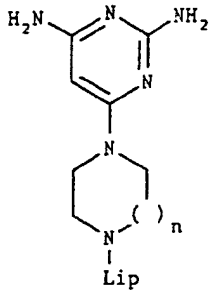
is formed from the compound of the general formula (XVIII) above by reaction with isonitrosomalonitrile using e.g. the method described by E. C. Taylor et al. [J. Am. Chem. Soc. 81, 2442 (1959)]. Finally the salt of the general formula (XIX) thus obtained is isomerized to the desired intermediate of the general formula (X) by heating it with a suitable base, such as an alkali metal hydroxide or alkali metal carbonate.

It should be noted that the last step (isomerization) of the preparation of compounds of the general formula (X) and the subsequent reaction with benzyl cyanide to give the compounds of the general formula (I) can conveniently be carried out in the same reaction mixture without isolation of the compound of the general formula (X), e.g. in the manner described in the Hungarian patent specification No. 195,815.

Process g)

The compounds of the general formula (XI) may be reacted with benzyl cyanide under the conditions described for process e) and a protective group eventually present may similarly be removed e.g. in the way described therein.

The starting substances of the general formula (XI) may be prepared e.g. in such a way that a compound of the general formula (XX),



(XX)

wherein

Lip and n are as defined for the general formula (I) in the introduction, with the proviso that Lip may not be hydrogen,

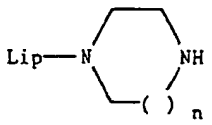
is treated with nitrous acid by using the method described in the above-cited paper of H. Sato et. al., see the discussion of process e).

The compounds of the general formula (XX) used as starting substances can be prepared from 4-chloro-2,6-diaminopyrimidine and an appropriate compound of the general formula (Va) in a manner known per se (see the British patent specification No. 2,198,132).

Process h)

The compounds of general formula (XII) can be reacted with 5-nitroso-2,4,6-triaminopyrimidine of the formula (IX) e.g. under the conditions described for process e); and a protective group eventually present may be removed similarly to the method described therein.

The starting substances of the general formula (XII) may be prepared from ethyl cyanoacetate and the appropriate compound of the general formula (Va)



(Va)

wherein

Lip and n are as defined for the compounds of the general formula (I) in the introduction,

by using known methods [see e.g. T. S. Osdene et al., J. Med. Chem. 10, 165 (1967)].

The acid addition salts of the compounds of the general formula (I) may be prepared by using any general method known per se, e.g. by reacting a base of the general formula (I) with 1-4 equivalents of the desired acid in an inert organic solvent, water or in a mixture thereof and then isolating the salt obtained by any know. method (e.g. filtration, evaporation of the solvent, trituration with a solvent and/or precipitation with a non-solvent).

When a protective group is removed from a compound of the general formula (I) containing an amine protective group as Lip by using an acid, the corresponding acid addition salt of the compound of the general formula (I) containing hydrogen as Lip can directly be obtained.

The compounds of the general formula (I) of the present invention and their pharmaceutically acceptable acid addition salts are endowed with valuable biological activities. More particularly, these compounds inhibit the peroxidation of lipids and are thereby useful for the treatment and/or prevention of diseases and conditions in which the inhibition of the lipid peroxidation is desirable.

The lipid peroxidation inhibitory activity of the compounds of the present invention and of the pharmaceutically acceptable salts thereof was demonstrated and determined by biochemical and pharmacological studies. Hereinafter, several tests and the results obtained in these tests for the compounds of the invention will be described.

In these studies known lipid peroxidation inhibitors such as 3,5-di(tert-butyl)-4-hydroxytoluene ["butylated hydroxytoluene", BHT, see e.g. W. Snipes et al., Science 188, 64 (1975)], α-tocopherol (vitamin E, see e.g. the paper of M.J. Kelly cited above); further 21-[4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]-16a-methyl-pregna-1,4,9(11)-triene-3,20-dione [U74006F, see e.g. J. M. Braughler et al., J. Biol. Chem. 262, 10438 (1987)], and 2-[[4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]methyl]-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyrane [U78517F, see e.g. E. D. Hall et al., J. Pharmacol. Exp. Ther. 258, 688 (1991)] were used as reference compounds.

Biochemical investigations

1. The ferrous ion dependent lipid peroxidation inhibitory activity was measured on rat brain homogenate by using the method descibed by J. M. Braughler et al., [J. Biol. Chem. 262, 10438 (1987)] and J. A. Buege and S. D. Aust [Methods in Enzymology 52, 302 (1978)]. The IC_{50} values (expressed in micromols) of some compounds of the invention and those of the reference compounds determined in this test are summarized in Table 1 below. The IC_{50} value is defined as the concentration of a test substance which reduces by 50 % the amount of the thiobarbituric acid reactive substances (chiefly malondialdehyde) considered to be a characteristic parameter of lipid peroxidation.

Table 1

Compound (No. of Example)	IC_{50}, µM
Reference compounds	
BHT	1
α-tocopherol	7
U74006F	39
U78517F	0.3
Compounds of the invention	
1	30
3	52
9	51
12	18
20	94
22	13
23	9
26	19
27	8
30[1)]	12
33	20
36	30

[1)] Hydrogentartrate

2. The inhibition of the ferrous ion dependent peroxidation of arachidonic acid was also measured by the method of J.M. Braughler et al. [J. Biol. Chem. 262, 10438 (1987)] and J. A. Buege and S. D. Aust [Methods in Enzymology 52, 302 (1978)]. The IC_{50} values (expressed in micromols) of some compounds of the invention, further those of the reference compounds determined in this test are shown in Table 2.

Table 2

Compound(No. of Example)	IC_{50}, µM
Reference compounds	
BHT	>100
α-tocopherol	2
U74006F	>100
U78517F	> 50
Compounds of the invention	
37[1)]	17
50[1)]	15
51[1)]	28
52[1)]	12
53[1)]	0.9
54[1)]	17
57[2)]	49
58[2)]	38

[1)]Ditartrate

[2)]Hydrochloride

3. Inhibiton of the NADPH dependent lipid peroxidation was measured according to T. J. Player and A. A. Horton [J. Neurochem. 37, 422 (1981)] and Z. Duniec [Biochem. Pharmacol. 32, 2283 (1983)]. The IC_{50} values (expressed in micromols) of some compounds of the invention, further those of the reference compounds determined in this test are given in Table 3.

Table 3

Compound (No. of Example)	IC_{50}, μM
Reference compounds	
BHT	2
α-tocopherol	>100
U74006F	>100
U78517F	0.7
Compounds of the invention	
23	13
26	59
27	22
30[1)]	16

[1)] Hydrogentartrate

Pharmacological investigations

1. The compounds of the present invention as well as the reference compounds inhibited the acute brain injury of mice described by E. D. Hall et al. [J. Neurosurg. 68, 456 (1988)]. The doses of the test compounds administered by the intravenous route and the percentage of improvement in the neurological state are summarized in Table 4.

Table 4

Compound (No. of Example)	Dose, mg/kg	Improvement, %
Reference compounds		
α-tocopherol	30	97
U74006F	30	77
U78517F	20	31
Compounds of the invention		
1	10	68
12	10	46
27	20	82
50[1)]	20	93

[1)] Ditartrate

2. In the test described by D. A. Parks et al. [Surgery 92, 896 (1982)] the compounds of the invention inhibited the ischemia induced weight increase of a definite section in the small intestine of rats. The percentage of inhibition observed after administration of a 25 mg/kg oral dose of the compounds of the invention or of the reference compounds is shown in Table 5.

Table 5

Compound(No. of Example)	Inhibition, %
Reference compounds	
α-tocopherol	-
U74006F	59
U78517F	20
Compounds of the invention	
1	55
3	31
4	46
6	25
7	34
9	37
10	56
11	57
12	52
15	32
16	45
18[1)]	31
20	28
23	52
24	20
25	35
26	45
27	60

Table 5 (continued)

Compound (No. of Example)	Inhibition, %
28	64
30[2)]	42
31	79
33	53
34	69
36	24
37[3)]	35
39	34
50[3)]	78
52[3)]	34
53[3)]	56
54[3)]	56
55[3)]	47
56[3)]	44
59[3)]	30

[1)] Hydrochloride

[2)] Hydrogentartrate

[3)] Ditartrate

Toxicity

The acute toxicity of certain compounds of the invention was determined in rats and generally it was found to be favourably low. Thus e.g. a 1000 mg/kg oral dose of the compounds of Examples 1, 10, 27, 28, 34 and 50 did not provoke death of any of the treated animals (i.e. LD_{50} > 1000 mg/kg), similarly to the toxicity measured for the reference compound U74006F mentioned above.

The above data demonstrate that several compounds of the general formula (I) of the present invention inhibit the peroxidation of lipids in vitro. Thereby these compounds are capable to suppress various pathological processes accompanied by an increased rate of lipid peroxidation in the living organism as it was proven by the results of the above in vivo investigations. In addition, this favourable activity is accompanied by low toxicity.

For therapeutic purposes the compounds of the present invention and their pharmaceutically acceptable salts may be used alone or preferably in the form of pharmaceutical compositions. Such compositions contain as active ingredient a compound of the general formula (I) or its pharmaceutically acceptable acid addition salt in an amount which is sufficient to produce the desired effect, in admixture with known carriers, excipients, diluents and/or other additives commonly used in the pharmaceutical practice.

The present invention also relates to a method for inhibiting the peroxidation of lipids and for treating diseases and conditions wherein the inhibition of lipid peroxidation is desirable. This method comprises of administering a therapeutically effective amount of an active ingredient of the formula (I) or of its pharmaceutically acceptable salt to a patient in need of such treatment.

Although the therapeutically effective dose of the compounds of the present invention may vary and depend upon the condition and age of each individual patient to be treated and will ultimately be determined by the attending physician, generally a daily oral dose of these compounds between about 0.1 mg and about 100 mg per kg body weight may be used for the prevention and/or treatment of diseases wherein inhibition of lipid

peroxidation is desirable.

The present invention is further illustrated in detail by the following non-limiting examples.

Example 1

1-(10-Undecenoyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine

To a solution of 1-[2,6-di(l-pyrrolidinyl)-4-pyrimidinyl]piperazine (2.25 g, 7.4 mmol) in anhydrous pyridine (45 ml) 10-undecenoyl chloride (1.85 ml, 1.75 g, 8.6 mmmol) was added dropwise under stirring at 0-5 °C. The reaction mixture was stirred at the same temperature for one hour and then poured into 450 ml of water. After 15 minutes of stirring the yellow powderlike precipitate was collected, washed with water and dried. Recrystallization of this crude product from acetonitrile afforded 2.86 g of the title compound, yield : 82.0 %, mp. 93-96 °C.

The starting 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine can be prepared e.g. as described in the literature (published PCT application WO 87/01706).

The 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]homopiperazine was prepared in a similar manner, yield : 68.4 %, mp. 106-110 °C.

Example 2

1-(n-Octadecanoyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine

By following the procedure of Example 1, with the difference that n-octadecanoyl chloride was used instead of 10-undecenoyl chloride, the title compound was obtained in a yield of 50.0 %, mp. 102-104 °C.

Example 3

1-(10-Undecenoyl)-4-(2,6-diamino-4-pyrimidinyl)-piperazine

A mixture of 1-(2,6-diamino-4-pyrimidinyl) piperazine-bis- trifluoroacetate (1.26 g, 3.0 mmol) and anhydrous potassium carbonate (1.38 g, 10.0 mmol) in acetonitrile (120 ml) was stirred under reflux for 30 minutes. Then 10-undecenoyl chloride (0.74 ml, 0.70 g, 3.4 mmol) was added dropwise and stirring under reflux was continued for one hour. After cooling the solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride (100 ml) and water (100 ml). The aqueous layer was separated and extracted twice with methylene chloride (40 m) each). The combined organic extracts were washed with water twice (until neutral), dried over $MgSO_4$ and concentrated under reduced pressure. The obtained crude product was triturated with isopropyl ether. In this manner 1.5 g of the title compound was obtained as a crystalline substance, yield : 69.4 %, mp. 100-104 °C.

The starting 1-(2,6-diamino-4-pyrimidinyl)piperazine-bistrifluoroacetate was prepared by following step c) of Example 60 and deprotecting thus 1-(tert-butoxycarbonyl)-4-(2,6-diamino-4-pyrimidinyl)piperazine which in turn was prepared as described in step a) of Example 59. Mp. of the obtained bis-trifluoroacetate : 192-198 °C, yield : 98.7 %.

The analogous 1-(2,6-diamino-4-pyrimidinyl)homopiperazine was prepared by reaction of 2,6-diamino-4-chloropyrimidine with unprotected homopiperazine (5 mol equivalents) in ethanol in a sealed tube, following the procedure of Example 19. Yield of the obtained base : 91.3 %, mp. 62-72 °C.

Examples 4-8

By using appropriate starting compounds, the procedure of Example 3 was followed to prepare the compounds of formula (I) listed in Table 6, wherein
each of A^1 and A^2 stand for a single bond,
Lip and n are as given in the Table and
Het represents a group of the general formula (a) wherein
R^1 is as given in the Table.

Table 6

No. of Example	Lip	n	R^1	Mp., °C	Yield, %
4	octadecyl	1	NH_2	121-123	54.5
5	octadecyl	1	1-pyrrolidinyl	75-77	68.2[1)]
6	octadecanoyl	2	1-pyrrolidinyl	63-66	95.0[1)]
7	octadecanoyl	1	NH_2	110-114	88.4
8	9-octadecenoyl	1	1-pyrrolidinyl	75-82	45.1[1)]

[1)]The base form of the starting piperazine derivative was used, in the presence of 2 mol equivalents of K_2CO_3.

Example 9

1-Trityl-4-(2,6-diamino-4-pyrimidinyl) piperazine

A mixture of 1-(2,6-diamino-4-pyrimidinyl)piperazine-bistrifluoroacetate (2.1 g. 5.0 mmol), potassium carbonate (1.0 g, 7.5 mmol) and trityl chloride (1.36 g, 5.0 mmol) in acetonitrile (50 ml) was stirred vigorously at room temperature. After 3 hours the solvent was evaporated under reduced pressure and the solid residue was stirred with 100 ml of water at room temperature for one hour. The yellow powderlike substance was collected, washed with water and dried. This crude product was purified by column chromatography over silica gel eluting with a 9:1 mixture of methylene chloride and methanol to give 0.88 g of the title compound, yield : 40.4 %, mp.152-160 °C.

Example 10-14

By using appropriate starting compounds, the procedure of Example 9 was followed to prepare the compounds of formula (I) listed in Table 7, wherein
each of A^1 and A^2 stand for a single bond,
Lip and n are as given in the Table and
Het represents a group of the general formula (a) wherein
R^1 is as given in the Table.

Table 7

No. of Example	Lip	n	R^1	Mp.,°C	Yield,%
10	trityl	1	1-pyrrolidinyl	246-250	33.5
11	trityl	2	1-pyrrolidinyl	215-218	59.1
12	o-chlorotrityl	1	NH_2	160-170	62.0
13	o-chlorotrityl	1	1-pyrrolidinyl	242-250	54.2
14	o-chlorotrityl	2	1-pyrrolidinyl	151-152	46.6

Examples 15-17

By using appropriate starting compounds, the procedure of Example 9 was followed to prepare the compounds of formula (I) listed in Table 8, wherein each of A^1 and A^2 stand for a single bond and Lip, Het and n are as given in the Table.

Table 8

No. of Example	Lip	n	Het	Mp., °C	Yield, %
15	o-chlorotrityl	1	4,7-diamino-6-phenyl-2-pteridinyl	250-252	56.8[1)]
16	o-chlorotrityl	1	2,4,7-triamino-6-pteridinyl-carbonyl	>260 (dec.)	51.6[2)]
17	o-chlorotrityl	1	4-amino-6,7-dimethoxy-2-quinazolinyl	164-168	73.7

[1)] Starting with the compound of Example 58
[2)] Starting with the compound of Example 60

Example 18

1-(1-Adamantyl)-4-(4-chloro-3-oxo-2,3-dihydro-5-pyridazinyl)-piperazine

A mixture of 1-(1-adamantyl)piperazine (2.2 g, 10 mmol), triethylamine (1.36 ml, 10 mmol) and 4,5-dichloro-3-oxo-2,3-dihydro-pyridazine (1.65 g, 10 mmol) in ethanol (25 ml) was heated under reflux for 5 hours. After cooling the precipitated solids were collected, washed with ethanol and dried to afford 2.57 g of the title compound, yield : 73.6 %, mp. 292-294 °C.

The above product was dissolved in a hot mixture of ethanol (25 ml), water (6 ml) and conc. HCl (2 ml), and the solution was treated with decolorizing carbon. After filtration, upon cooling the hydrochloride of the title compound separated as colorless crystals, yield : 2.0 g, mp. 306-308 °C.

Example 19

1-(1-Adamantyl)-4-(2,6-diamino-4-pyrimidinyl)-piperazine

A mixture of 2,6-diamino-4-chloropyrimidine (0.43 g, 3.0 mmol) and 1-(1-adamantyl)-piperazine (0.66 g, 3.0 mmol) in ethanol (30 ml) was heated in a sealed tube at 170 °C for 3 hours. After cooling the solvent was removed, the solid residue was dissolved in water (45 ml) and acidified to pH=3 with conc. HCl. The obtained mixture was heated to 50 °C, the insolubles were filtered off, and the clear solution was rendered alkaline with 10 N NaOH under stirring and cooling. The precipitated crystals were collected, washed with water until neutral and dried. In this manner 0.79 g of the title compound was obtained in the form of its monohydrate, yield : 76.6%, mp. 265-268 °C.

Example 20

1-[2-Hydroxy-3-(1-naphthyloxy)-propyl]-4-(2,6-diamino-4-pyrimidinyl)piperazine

A mixture of 1-(2,6-diamino-4-pyrimidinyl)piperazine-bis- trifluoroacetate (0.85 g, 2.0 mmol) and potassium carbonate (0.69 g, 5.0 mmol) in ethanol (60 ml) was stirred under reflux for 30 minutes. The mixture was filtered hot and to the filtrate a solution of 1,2-epoxy-3-(1-naphthyloxy)-propane (0.6 g, 3.0 mmol) in ethanol (10 ml) was added. The mixture was heated under reflux for 3 hours, the solvent was evaporated and the residue was partitioned between ethyl acetate (80 ml) and water (80 ml). The aqueous layer was separated and extracted with ethyl acetate (40 ml). The combined organic extracts were washed once with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column eluting with a 75:20:5 mixture of ethyl acetate, methanol and conc. NH_4OH. In this manner 0.58 g of the title compound was obtained as a foam, yield : 74.3 %. Mp. after trituration with isopropyl ether : 122-124 °C.

The starting epoxide of formula (IV) wherein Lip stands for 1-naphthyloxy can be prepared by a known method, see E. Fourneau, M. Trefouel, Bull. Soc. chim. France [4], 43, 454 (1928).

Examples 21-30

By using appropriate starting compounds, the procedure of Example 20 was followed to prepare the compounds of formula (I) listed in Table 9, wherein

A^1 stands for 2-hydroxy-1,3-propylene,

A^2 stands for a single bond,

Lip and n are as given in the Table and

Het represents a group of the general formula (a) wherein

R^1 is as given in the Table.

Table 9

No. of Example	Lip	n	R^1	Mp., °C	Yield,
21	1-naphthyloxy	2	NH_2	120-125	39.2
22	1-naphthyloxy	1	1-pyrrolidinyl	132-138	63.4
23	1-naphthyloxy	2	1-pyrrolidinyl	56-58	61.2
24	2-naphthyloxy	1	NH_2	224-228	67.8
25	2-naphthyloxy	2	NH_2	57-63	39.3
26	2-naphthyloxy	1	1-pyrrolidinyl	145-147	48.7
27	2-naphthyloxy	2	1-pyrrolidinyl	102-106	72.9
28	1-oxo-1,2,3,4-tetrahydro-6-naphthyloxy	1	NH_2	194-197	28.5
29	1-oxo-1,2,3,4-tetrahydro-6-naphthyloxy	1	1-pyrrolidinyl	146-150	64.1
30	1-oxo-1,2,3,4-tetrahydro-6-naphthyloxy	2	1-pyrrolidinyl	182-186[1)]	62.5

[1)] Hydrogentartrate

1,2-Epoxy-2-(2-naphthyloxy)-propane (mp. 51-56 °C, yield : 52.7 %) and 1,2-epoxy-3-(1-oxo-1,2,3,4-tetrahydro-6-naphthyloxy)propane (oil, yield : 87.9 %) used as starting compounds in Examples 24-30 were prepared by the method of E. Fourneau and M.Trefouel cited above.

Example 31

1-[2-(1-Naphthyloxy)acetyl]-4-(2,6-diamino-4-pyrimidinyl)-piperazine

A suspension of 1-(2,6-diamino-4-pyrimidinyl)piperazine-bis- trifluoroacetate (1.1 g, 2.5 mmol) and potassium carbonate (1.38 g, 10 mmol) in acetonitrile (100 ml) was stirred vigorously under reflux for 30 minutes. Then a solution of 2-(1-naphthyloxy)acetyl chloride (0.65 g, 3.0 mmol) in acetonitrile (5 ml) was added dropwise and the mixture was heated under reflux for one hour. Thereafter the insolubles were filtered off while hot and the filtrate was concentrated. The residue was stirred with 100 ml of water for one hour, the precipitate formed was collected, washed with water until neutral and dried to give 0.90 g of the title compound, yield : 59.2 %, mp. 205-210 °C.

Example 32

1-[2-(2-Naphthyloxy)acetyl]-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]homopiperazine

To a solution of 2-(2-naphthyloxy)acetic acid (1.1 g, 5.0 mmol) in anhydrous tetrahydrofuran (25 ml) carbonyl-diimidazole (0.80 g, 5.0 mmol) was added in portions, under stirring at room temperature. After 15 minutes a solution of 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]homopiperazine (1.58 g, 5.0 mmol) in anhydrous tetrahydrofuran (15 ml) was added dropwise. The mixture was stirred at room temperature for 8 hours and the sol-

vent was distilled off under reduced pressure. The residue was dissolved in methylene chloride, the solution was washed three times with water, dried over $MgSO_4$ and concentrated. The obtained crude product was chromatographed over a silica gel column eluting with a 1:2 mixture of benzene and ethyl acetate to afford 0.7 g of the title compound, yield: 28 %, mp. 103-110 °C.

Example 33

1-[2-(1-Naphthyloxy)acetyl]-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine

Metallic sodium (0.069 g, 3 mg-atom) was dissolved in anhydrous ethanol (4 ml) and the obtained solution was added to a mixture of 1-naphtol (0.36 g, 2.2 mmol) and 1-(2-chloroacetyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine ((0.9 g, 2.4 mmol) in ethanol (30 ml). The reaction mixture was heated under reflux for 4 hours, cooled to room temperature and the insolubles were filtered off. The filtrate was concentrated to dryness and the residue was chromatographed over a silica gel column eluting with a 1:2 mixture of benzene and ethyl acetate. By triturating the obtained product with isopropyl ether 0.75 g of the title compound was obtained, yield : 72.0 %, mp. 156-160 °C.

The starting 1-(2-chloroacetyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine was prepared as follows : 1-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine (1.65 g, 5.4 mmol) was dissolved in anhydrous chloroform (30 ml), the solution was cooled to 0-5 °C and 2-chloroacetyl chloride (0.50 ml, 0.79 g, 7.0 mmol) in anhydrous chloroform (5 ml) was added dropwise under stirring. The mixture was stirred for one-hour, concentrated and the residue was dissolved in 100 ml of water. The aqueous solution was made alkaline with conc. NH_4OH and stirred for one hour. During this period the separated oil solidified. The solids were collected, washed with ice-cold water until neutral and dried. In this manner 2.0 g of the desired chloroacetyl compound was obtained, yield : 97.0 %, mp. 153-156 °C.

1-(2-Chloroacetyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]-homopiperazine was prepared in a similar manner and was obtained as a tan viscous oil, yield : 98.2 %.

Examples 34-36

By using appropriate starting compounds, the procedure of Example 31 or 32 was followed to prepare the compounds of formula (I) listed in Table 10, wherein
A^1 stands for CH_2CO,
A^2 stands for a single bond,
Lip and n are as given in the Table and
Het represents a group of the general formula (a) wherein
R^1 is as given in the Table.

Table 10

No. of Example	Lip	n	R^1	Method (Example)	Mp.,°C	Yield,%
34	2-naphthyloxy	1	NH_2	31	100-103	52.9
35	2-naphthyloxy	1	1-pyrrolidinyl	31	153-156	48.0
36	1-naphthyloxy	2	1-pyrrolidinyl	32	135-140	51.3

Example 37

6-[4-[3-[4-(1-Adamantyl)-1-piperazinyl]-2-hydroxypropoxyl]phenyl]-2,4,7-triaminopteridine

A mixture of 4-[3-[4-(1-adamantyl)-1-piperazinyl]-2-hydroxy-propoxy]benzylcyanide (3.44 g, 8.4 mmol), 5-nitroso-2,4,6-triamino-pyrimidine (1.08 g, 7.0 mmol) and 0.2 N sodium-(2-ethoxyethoxide) in 2-ethoxyethanol (35 ml) was stirred at 120 °C for 30 minutes. After cooling to about 90 °C 100 ml of water was added and the mixture was cooled to room temperature followed by stirring in an ice-water bath for 30 minutes. The precipitate was collected, washed with water and acetonitrile to give the title compound (3.23 g) as a yellow powder, mp. 287-289 °C (dec.), yield : 84.6 %.

0.27 g (0.5 mmol) of the above product was dissolved in a hot solution of L(+)-tartaric acid (0.23 g, 1.5 mmol) in water (1 ml), and the obtained solution was allowed to cool. The precipitated crystals were collected,

washed with acetonitrile and dried to give the ditartrate pentahydrate of the title compound, mp. 165-175 °C, yield of the salt formation : 38.3 %.

The starting 4-[3-[4-(1-adamantyl)-1-piperazinyl]propoxy]benzyl-cyanide was prepared as follows : A solution of 1-(1-adamantyl)piperazine (4.4 g, 20 mmol) 4-(2,3-epoxypropoxy)benzylcyanide (2.9 g, 15.4 mmol) in methanol (45 ml) was stirred at room temperature for 4 hours. Then the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. Trituration of the residue afforded 3.67 g of the desired substituted benzylcyanide as pale yellow crystals, yield : 45.8 %, mp. 136-138 °C.

Example 38

6-[4-[2-Hydroxy-3-[4-(tert-butoxycarbonyl)-1-piperazinyl]propoxy]phenyl]-2,4,7-triaminopteridine

Sodium metall (0.22 g, 9.6 mg-atom) was dissolved in 2-ethoxyethanol (60 ml) at 40-50 °C, the solution was cooled to room temperature and 5-nitroso-2,4,6-triamino-pirimidine (1.46 g, 9.5 mmol) was added, followed by 4-[2-hydroxy-3-[4-(tert-butoxycarbonyl)-1-piperazinyl]propoxy]benzylcyanide (3.92 g, 10.4 mmol) prepared as described in Example 45. The mixture was stirred under reflux in an atmosphere of nitrogen for one hour and the obtained dark brown solution was cooled to room temperature. After dilution with 200 ml of ethyl acetate the precipitate was collected, washed with ethyl acetate and dried to yield a yellow powder, mp. 244-246 °C (dec.). The filtrate was concentrated and the residue was dissolved in 30 ml of methanol. After treatment with decolorizing carbon the solution was concentrated to a volume of 10 ml and the separated crystals were collected. Total yield of the two generations : 84.8 %.

Examples 39-44

By using appropriate starting compounds, the procedure of Example 38 was followed to prepare the compounds of formula (I) listed in Table 11, wherein
Lip is o-chlorotrityl (o-Cl-Tr) or tert-butoxycarbonyl (Boc),
A^1 stands for a single bond,
n and A^2 are as given in the Table and
Het represents a group of the general formula (g) wherein
X is as given in the Table.

Table 11

No. of Example	Lip	n	A^2	X	Mp., °C	Yield,%
39	o-Cl-Tr	1	$CH_2CH(OH)CH_2$	O	220-228	62.5[1)]
40	Boc	2	$CH_2CH(OH)CH_2$	O	238-240	84.2
41	Boc	1	$CH_2CH(OH)CH_2$	NH	240-241	45.7
42	Boc	1	$CH_2CH(OH)CH_2$	$N(CH_3)$	233-235	62.1
43	Boc	1	$CH_2CH(OH)CH_2$	S	250-251	74.7[1)]
44	Boc	1	CH_2CO	NH	275-280	68.3[2)]

[1)] By using 4 equivalents of NaOH as base instead of sodium-(2-ethoxy-ethoxide)
[2)] At 100 °C

The compounds of formula (VIII) used as staring materials in Examples 38-44 were prepared as described in Examples 45-49 below.

Example 45

4-[2-Hydroxy-3-[4-(tert-butoxycarbonyl)-1-piperazinyl]propoxy]benzylcyanide

A solution of 4-(2,3-epoxypropoxy)benzylcyanide (2.84 g, 15 mmol) and 1-(tert-butoxycarbonyl)piperazine (4.2 g, 22.5 mmol) in methanol (35 ml) was stirred at room temperature for 3 hours and the solvent was removed. The residue was dissolved in 200 ml of ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated. The obtained crude product was chromatographed on a silica gel column eluting with ethyl acetate. The obtained sticky material was triturated with hexane to give 3.95 g of the title compound, yield : 70.2 %, mp. 98-100 °C.

Similarly was prepared the 4-[2-hydroxy-3-[4-(tert-butoxycarbonyl)-1-homopiperazinyl]propoxy]benzylcyanide, it was obtained in a yield of 69.9 % as an oil [starting with 1-(tert-butoxycarbonyl)homopiperazine which was in turn obtained in a yield of 38.8 % as an oil by following the procedure described for the analogous piperazine derivative in the published German patent application 2,550,111].

4-[2-Hydroxy-3-[4-(o-chlorotrityl)-1-piperazinyl]propoxy]benzyl- cyanide was also prepared in a similar manner, yield : 63.8 %, mp. 103-106 °C. [The starting substance for the preparation of this latter compound, i.e. 1-(o-chlorotrityl)-piperazine was prepared from 1-formylpiperazine, by first alkylating with 1 mol equivalent of trityl chloride in acetonitrile in the presence of 1 mol equivalent of potasssium carbonate (3 hours at room temperature) and the obtained 1-formyl-4-(o-chlorotrityl)-piperazine (mp. 245-247 °C, yield : 89.5 %) was deformylated by refluxing with an equal weight of NaOH in butanol for 90 minutes, yield : 82.0 %, mp. 178-180 °C.]

Example 46

4-[2-Hydroxy-3-[4-(tert-butoxycarbonyl)-1-piperazinyl]propyl-amino]benzylcyanide

Step a)

4-(2,3-Epoxypropyl-amino)benzylcyanide

A mixture of 4-aminobenzylcyanide (10 g, 75.7 mmol), epichlorohydrine (7.9 ml, 9.25 g, 100 mmol), ethanol (15 ml) and water (10 ml) was heated under reflux for 2 hours. After cooling the reaction mixture was poured into 100 ml of water and extracted with ether (3 x 50 ml). The organic extracts were combined and stirred with 50 ml of 10 N NaOH at room temperature for 3 hours. The organic layer was separated, washed with water until neutral, dried over $MgSO_4$ and concentrated. The residue was chromatographed over a silica gel column eluting with a 3:1 mixture of benzene and ethyl acetate to afford 7.24 g of the title compound as an oil, yield : 51.0 %.

Step b)

4-[2-Hydroxy-3-[4-(tert-butoxycarbonyl)-1-piperazinyl]propyl-amino]benzylcyanide

A solution of the epoxide obtained as described in step a) above (4.96 g, 26.4 mmol) and 1-(tert-butoxycarbonyl)piperazine (6.4 g, 34.4 mmol) in methanol (30 ml) was heated under reflux for 2 hours, and the product was isolated as described in Example 45.

The obtained crude product was chromatographed over a silica gel column eluting with a 9:1 mixture of ethyl acetate and methanol to give the title compound (3.68 g), mp. 86-87 °C, yield : 37.2 %.

Example 47

4-[N-Methyl-N-[2-hydroxy-3-[4-(tert-butoxycarbonyl)-1-piperazinyl]propyl]amino]benzylcyanide

Step a)

4-[N-Methyl-N-(2,3-epoxypropyl)amino]benzylcyanide

A mixture of 4-methylaminobenzylcyanide (3.05 g, 20.9 mmol), epichlorohydrine (2.4 ml, 2.87 g, 31 mmol), ethanol (25 ml) and water (20 ml) was heated under reflux for 3 hours. After cooling the mixture was diluted with ethanol (10 ml) followed by addition of aqueous 10 N NaOH (6 ml). The obtained clear solution was stirred at room temperature for one hour and the ethanol was distilled off. The residue was diluted with 100 ml of water and extracted with ether (3 x 50 ml). The organic extracts were washed with brine until neutral, dried over $MgSO_4$ and concentrated. The residue was chromatographed over a silica gel column eluting with a 3:1 mixture

of benzene and ethyl acetate to give 2.21 g of the oily title compound, yield : 52.2 %.

Step b)

4-[N-Methyl-N-[2-hydroxy-3-[4-(tert-butoxycarbonyl)-1-piperazinyl]propyl]amino]benzylcyanide

The epoxide prepared as described in step a) above (2.21 g, 10.9 mmol) was allowed to react with 1-(tert-butoxycarbonyl)-piperazine (3.05 g, 16.4 mmol) by following the procedure of step b) of Example 46 and the product was isolated as described therein. In this manner 4.02 g of the title compound was obtained as an oil, yield : 94.8 %.

Example 48

4-[2-Hydroxy-3-[4-(tert-butoxycarbonyl)-1-piperazinyl]propyl-thio]benzylcyanide

Step a)

4-(N,N-Dimethylthiocarbamoyloxy)benzylcyanide

Metallic sodium (1.15 g, 50 mg-atom) was dissolved in methanol (100 ml) and 4-hydroxybenzylcyanide (6.7 g, 50 mmol) was added.

The obtained solution was concentrated and acetonitrile (2 x 10 ml) was evaporated from the residue. The obtained salt was dissolved in anhydrous dimethylformamide (200 ml) and about 25 ml of the solvent was removed under reduced pressure. To the obtained solution N,N-dimethylthiocarbamoyl chloride (9.9 g, 80 mmol) was added and the reaction mixture was stirred at 80-85 °C for 2 hours. Thereafter additional N,N-dimethylthiocarbamoyl chloride (2.5 g, 20 mmol) was added and stirring at 80 °C was continued for further one hour. After cooling the mixture was poured into aqueous 1 % KOH (500 ml) and extracted with ether (3 x 200 ml). The organic extracts were washed with water until neutral, dried over $MgSO_4$ and concentrated. The solid residue was triturated with water and after drying also with isopropyl ether to give the title compound (5.42 g), mp. 120-124 °C, yield : 52.7 %.

Step b)

4-(N,N-Dimethylcarbamoylthio)benzylcyanide

To Dowtherm A (75 ml) preheated to 250 °C, under nitrogen' the compound prepared as described in step a) above (5.05 g, 22.9 mmol) was added and the mixture was stirred at the same temperature for one hour. After cooling the reaction mixture was diluted with 200 ml of benzene, treated with decolorizing carbon and the solvents were distilled off under reduced pressure. The residue was chromatographed on a silica gel column eluting with a 3:1 mixture of benzene and ethyl acetate to afford the title compound (3.08 g) as yellow crystals, yield : 60.1 %, mp. 97-99 °C.

Step c)

1-(2,3-Epoxypropyl)-4-(tert-butoxycarbonyl)piperazine

A solution of 1-(tert-butoxycarbonyl)piperazine (18.6 g, 100 mmol) and epichlorohydrine (10.2 ml, 12.0 g, 130 mmol) in methanol (50 ml) was stirred at room temperature for 24 hours and the solvent was evaporated. The residue was dissolved in 200 ml of ether and the solution was stirred with 10 N aqueous NaOH (100 ml) at room temperature for 2 hours. Then the organic layer was separated, washed with brine until neutral, dried over $MgSO_4$ and concentrated to afford the title compound (21.8 g) as a pale yellowish viscous oil, yield : 90.1 %.

Step d)

4-[2-Hydroxy-3-[4-(tert-butoxycarbonyl)-1-piperazinyl]propyl-thio]benzylcyanide

A mixture of the product of step b) above (3.08 g, 14 mmol), the epoxide prepared as described in step c) above (3.4 g, 14 mmol), ethanol (70 ml) and 2 N aqueous NaOH (7 ml) was heated under reflux in an atmosphere of nitrogen for 2 hours. After cooling the mixture was poured into 300 ml of water and extracted with ethyl acetate (2 x 150 ml). The organic layer was washed with brine until neutral, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column eluting with ethyl acetate to give 1.69 g of the title compound as a colorless solid, yield : 30.8 %. Mp. after trituration with hexane : 69-70 °C.

Example 49

4-[2-[4-(Tert-butoxycarbonyl)-1-piperazinyl]acetylamino]benzylcyanide

Step a)

4-(2-Chloroacetylamino)benzylcyanide

2-Chloroacetyl chloride (3.3 ml, 5.0 g, 44 mmol) was added dropwise at 10-15 °C to a solution of 4-aminobenzylcyanide (5.3 g, 40 mmol) in dimethyl acetamide (20 ml) and the mixture was stirred at room temperature for one hour. After pouring into water the precipitate was collected, washed with water and dried over P_2O_5 under reduced pressure to give the title compound (7.33 g) as nearly colorless crystals, yield : 87.8 %, mp. 124-125 °C.

Step b)

4-[2-[4-(Tert-butoxycarbonyl)-1-piperazinyl]acetylamino]benzyl-cyanide

A mixture of the product obtained according to step a) above (2.1 g, 10 mmol), 1-(tert-butoxycarbonyl)piperazine (2.4 g, 13 mmol) and potassium carbonate (1.8 g, 13 mmol) in acetonitrile (50 ml) was stirred under reflux for 2 hours. After cooling the mixture was poured into water. The precipitate was collected, washed with water and dried under reduced pressure over P_2O_5 to afford 3.48 g of the title compound as nearly colorless crystals, yield : 97.2 %, mp. 137-138 °C.

Example 50

6-[4-[2-Hydroxy-3-(1-piperazinyl)propoxy]phenyl]-2,4,7-triamino-pteridine

Method A)

A mixture of the protected compound obtained according to Example 38 (5.5 g, 10.8 mmol) and 10 % aqueous HCl (140 ml) was stirred at room temperature for 20 hours. The yellow suspension was diluted with 350 ml of water and heated to about 40 °C. The obtained solution was filtered and made alkaline with 5 N aqueous NaOH. The formed precipitate was collected, washed with water until neutral and dried to give the title compound (4.4 g) as pale yellow crystals, yield : 100 %, mp. 245-255 °C.

3.91 g (9.5 mmol) of the above product was added to a solution of L(+)-tartaric acid (3.54 g, 23.6 mmol) in water (60 ml) and the solids were dissolved by heating to reflux. The hot solution was treated with decolorizing carbon, filtered and allowed to cool. The separated crystals were collected, washed with water and acetonitrile and dried to give the ditartrate-trihydrate of the title compound, mp. 185-190 °C, yield of the salt formation: 66.9 %.

Method B)

A suspension of the protected compound obtained according to Example 38 (1.5 g, 3 mmol) in a 1.5 N solution of HCl in ethyl acetate (20 ml) was stirred for 5 hours at room temperature. The solids (HCl salt of the title product) were then collected and after drying dissolved in water. The solution was made alkaline with aqueous 5 N NaOH and the precipitated base was filtered off to give the title compound which was identical with the product obtained according to Method A)-above, yield : 37.0 %.

Method C)

A mixture of the protected compound obtained according to Example 38 (0.26 g, 0.5 mmol) and L(+)-tartaric acid (0.23 g, 1.5 mmol) in water (2.5 ml) was heated under reflux for one hour and allowed to cool to room temperature. The separated precipitate was collected to give the ditartrate-trihydrate of the title compound which was identical with the salt obtained according to Method A) above, yield : 65.8 %, mp. 169-175 °C.

Examples 51-55

By using the appropriate starting compounds prepared according to Examples 40-44, the procedure of Example 50 was followed to prepare the compounds of formula (I) listed in Table 12, wherein

Lip is hydrogen,
A^1 stands for a single bond,
n and A^2 are as given in the Table and
Het represents a group of the general formula (g) wherein
X is as given in the Table.

Table 12

No. of Example	n	A^2	X	Method (Example)	Mp.,°C[1)]	Yield,%
51	2	$CH_2CH(OH)CH_2$	O	50/B	163-168	48.6[2)]
52	1	$CH_2CH(OH)CH_2$	NH	50/A	205-210[3)]	55.9
53	1	$CH_2CH(OH)CH_2$	$N(CH_3)$	50/B	175-180[4)]	68.1
54	1	$CH_2CH(OH)CH_2$	S	50/B	250-253[3)]	61.2
55	1	CH_2CO	NH	50/B	90-95[5)]	45.1

[1)]Ditartrate
[2)]By using 97 % HCOOH instead of HCl
[3)]Dihydrate ; [4)]Pentahydrate ; [5)]Heptahydrate

Example 56

6-[4-[3-(1-Piperazinyl)propylamino]phenyl]-2,4,7-triamino-pteridine

A mixture of 4-[3-(4-formyl-1-piperazinyl)propylamino]benzyl- cyanide (1.15 g, 4.0 mmol), 5-nitroso-2,4,6-triamino-pyrimidine (0.56 g, 3.6 mmol) and 0.2 N sodium-(2-ethoxy-ethoxide) in 2-ethoxyethanol (18 ml) was stirred under reflux for 3 hours, then NaOH (0.14 g, 3.5 mmol) was added and stirring under reflux was continued for further 2.5 hours. After cooling the mixture was diluted with 100 ml of ether. The separated precipitate was collected, washed with ether, then with water and dried to afford the title compound (0.92 g) as a yellow powder, yield: 64.8 %.

The above product was dissolved in a hot solution of L(+)-tartaric acid (0.75 g, 5 mmol) in water (6 ml) and after cooling the mixture was diluted with methanol (6 ml). The separated crystals were collected, washed with methanol and dried to give the ditartrate of the title compound, mp. 170-178 °C. Yield of the salt formation : 51.9 %.

The starting 4-[3-(4-formyl-1-piperazinyl)propylamino]benzyl-cyanide was prepared as follows :

Step a)

1-Formyl-4-(3-chloropropyl)piperazine

A mixture of 1-formylpiperazine (5.7 g, 50 mmol),1-bromo- 3-chloropropane (7.2 ml, 11.8 g, 75 mmol) and chlorobenzene (30 ml) was stirred at 100-105 °C for 3 hours. After cooling the separated 1-formylpiperazine hydrochloride (4.58 g, yield : 94.4 %) was filtered off and the filtrate concentrated. The residue was chromatographed on a silica gel column eluting with a 8:2 mixture of ethyl acetate and methanol to afford 2.46 g of the oily title compound, yield : 51.6 %.

Step b)

4-[3-(4-Formyl-1-piperazinyl)propylamino]benzylcyanide

A mixture of 1-formyl-4-(3-chloropropyl)piperazine (1.0 g, 5.2 mmol) prepared according to step a) above,

4-aminobenzyl-cyanide (0.66 g, 5 mmol) and sodium iodide (0.15 g, 1 mmol) was heated at 100-105 °C for 2 hours. After cooling the mixture was dissolved in 40 ml of water and treated with decolorizing carbon. The filtered solution was made alkaline with 2 N aqueous NaOH and extracted with chloroform (3 x 20 ml). The organic extracts were washed with water, dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column eluting with a 2:1 mixture of ethyl acetate and methanol to give the title compound. Yield : 0.55 g, 38.5 %. Mp. after trituration with ether : 85-87 °C.

Example 57

1-(1-Adamantyl)-4-(4,7-diamino-6-phenyl-2-pteridinyl)piperazine

Step a)

1-(1-Adamantyl)-4-amidinopiperazine hydroiodide

The title compound was prepared as described for 1-formylpiperazine in Example 1 of the published European patent application No. 39,190, starting with 1-(1-adamantyl) piperazine and S-methyl-isothiourea hydroiodide, mp. 278-280 °C, yield : 72.3 %.

Step b)

Isonitrosomalonitrile salt of 1-(1-adamantyl)-4-amidinopiperazine

A solution of sodium nitrite (0.74 g, 10.5 mmol) in water (1 ml) was added dropwise at 0-5 °C to a mixture of malonitrile (0.66 g, 10 mmol), water (1.2 ml) and acetic acid (0.7 ml) and the mixture was stirred first at the same temperature for 2 hours and then at room temperature for further 3 hours. Thereafter the reaction mixture was heated to 50 °C and a mixture of the hydroiodide prepared according to step a) above (3.12 g, 80 mmol) in methanol (6 ml), made alkaline with a 2 N ethanolic NaOEt solution was added. The obtained mixture was stirred at 80-85 °C for 2 hours, the insolubles were filtered off while hot, and the filtrate was concentrated. Trituration of the residue with water afforded 2.40 g of the crude title product, yield : 83.9 %. This crude product was dissolved in acetone, the insolubles were filtered off and the filtrate was concentrated to dryness to give the title compound in pure state, mp. 182-186 °C.

Step c)

1-(1-Adamantyl)-4-(4,7-diamino-6-phenyl-2-pteridinyl)piperazine

To a solution of the salt prepared as described in step b) above (0.50 g, 1.4 mmol) in 2-ethoxyethanol (7 ml) potassium carbonate (0.13 g, 0.9 mmol) was added and the mixture was heated under reflux for 90 minutes. After cooling to about 60 °C NaOH (0.08 g, 2 mmol) was added followed by the dropwise addition of benzyl-cyanide (0.25 ml, 2.2 mmol) in 2-ethoxyethanol (2 ml) at the same temperature. The mixture was stirred at 80 °C for 2 hours, cooled and diluted with 50 ml of water. The obtained precipitate was collected, washed with water and acetone to give the title compound (0.37 g), yield : 57.8 %, mp. 293-297 °C (dec.).

The above product was converted to its hydrochloride by using an ethyl acetate solution of anhydrous HCl, mp. >231 °C (dec.).

Example 58

1-(4,7-Diamino-6-phenyl-2-pteridinyl)piperazine

Step a)

1-(Tert-butoxycarbonyl)-4-amidinopiperazine hydroiodide

The title compound was prepared as described for 1-formylpiperazine in Example 1 of the published European patent application No. 39,190, starting with 1-(1-tert-butoxycarbonyl)-piperazine and S-methyl-isothiourea hydroiodide, mp. 180-182 °C, yield : 66.3 %.

Step b)

Isonitrosomalonitrile salt of 1-(tert-butoxycarbonyl)-4-amidino-piperazine

The title compound was prepared by following the procedure described in step b) of Example 57, starting

with the hydroiodide obtained according to step a) above, yield : 85.5 %, mp. 155-162 °C.

Step c)

1-(Tert-butoxycarbonyl)-4-(4,7-diamino-6-phenyl-2-pteridinyl)-piperazine

The title compound was prepared by following the procedure described in step c) of Example 57, starting with the salt obtained according to step b) above, yield : 40 %, mp. 240-242 °C.

Step d)

1-(4,7-Diamino-6-phenyl-2-pteridinyl)piperazine

A mixture of the protected compound prepared according to step c) above (3.8 g, 9 mmol) and 97 % formic acid (20 ml) was stirred at room temperature for 5 hours. The mixture was then poured into 200 ml of water and the pH was adjusted to 10 with 10 N NaOH. The separated solids were collected, dried and recrystallized from acetonitrile to afford the title compound (1.63 g), yield :
56.2 %, mp. 244-247 °C.

The above product was converted to its hydrochloride by using an ethyl acetate solution of anhydrous HCl, mp. 233-236 °C.

Example 59

1-(2,7-Diamino-6-phenyl-4-pteridinyl)piperazine

Step a)

1-(Tert-butoxycarbonyl)-4-(2,6-diamino-4-pyrimidinyl) piperazine

A mixture of 2, 6-diamino-4-chloropyrimidine (2.88 g, 20 mmol) and 1-(tert-butoxycarbonyl)piperazine (5.6 g, 30 mmol) in chlorobenzene (30 ml) was stirred under reflux for 3 hours. After cooling the formed precipitate was collected and stirred with aqueous 1 N NaOH (63 ml) at room temperature for 15 minutes. The solids were collected, washed with water and dried, yield : 90.4 %, mp. 176-179 °C.

Step b)

1-(Tert-butoxycarbonyl)-4-(2,6-diamino-5-nitroso-4-pyrimidinyl)-piperazine

A solution of sodium nitrite (4.24 g, 64.6 mmol) in water (43 ml) was added dropwise under 10 °C to a mixture of the product obtained according to step a) above (18.1 g, 64.6 mmol), and acetic acid (180 ml). The mixture was stirred for one hour and the precipitate was collected. This product was stirred with an aqueous 10 % solution of potassium carbonate (230 ml) at room temperature for one hour. The formed pink solids were collected, washed with water and dried at 100 °C, yield : 94.8 %, mp. 235-240 °C (dec.).

Step c)

1-(Tert-butoxycarbonyl)-4-(2,7-diamino-6-phenyl-4-pteridinyl)-piperazine

The title compound was prepared by reaction of the product obtained as described in step b) above with benzylcyanide, following the procedure of Example 37 with the difference that instead of sodium-(2-ethoxyethoxide) NaOH was used as a base. Mp. 245-246 °C, yield : 54.7 %.

Step d)

1-(2,7-Diamino-6-phenyl-4-pteridinyl)piperazine

By following Method B) of Example 50 deprotection of the compound obtained according to step c) above the title compound was obtained in a yield of 83.0 %, mp.(base) 265-275 °C.

The above product was converted to its ditartrate by following Method A) of Example 50, mp. 150-155 °C.

Example 60

1-(2,4,7-Triamino-6-pteridinylcarbonyl)piperazine

Step a)

1-(Tert-butoxycarbonyl)4-(2-cyanoacetyl)piperazine

A mixture of 1-(tert-butoxycarbonyl)piperazine (37.25 g, 0.20 mol) and ethyl cyanoacetate (22.6 g, 0.20 mol) was heated at 150-155 °C for 3 hours. After cooling the mixture solidified. Trituration with isopropyl ether afforded 24.7 g of the title compound, mp. 143-145 °C, yield : 48.8 %.

Step b)

1-(Tert-butoxycarbonyl)-4-(2,4,7-triamino-6-pteridinylcarbonyl)-piperazine

The title compound was prepared by following the procedure described in Example 37, by reaction of the compound obtained according to step a) above with 5-nitroso-2,4,6-triaminopyrimidine. Yield : 59.1 %, mp. 245-250 °C.

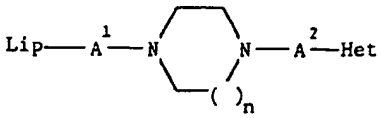
Step c)

1-(2,4,7-Triamino-6-pteridinylcarbonyl)piperazine

The protected compound obtained as described in step b) above was stirred with twofold (v/w) trifluoroacetic acid at 5-10 °C for one hour, diluted with tenfold (v/v) methanol and the precipitate was collected. In this manner the bis-trifluoroacetate of the title compound was obtained, mp. 233-238 °C, yield : 69.8 %.

Claims

1. Piperazine and homopiperazine derivatives of the general formula (I),



(I)

wherein

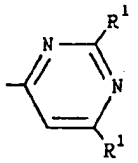
Lip stands for hydrogen; C_{15-20} alkyl; C_{10-20} alkanoyl or C_{10-20} alkenoyl; trityl optionally substituted by halogen; adamantyl; 1- or 2-naphthyloxy or oxo-substituted tetrahydronaphthyloxy; or an amine protective group commonly used e.g. in the peptide chemistry;

A^1 and A^2 are selected independently from the group consisting of a single bond and C_{2-3} alkylene optionally substituted by hydroxy or oxo;

n is 1 or 2; and

Het represents

a group of the general formula (a),

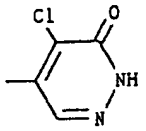


(a)

wherein

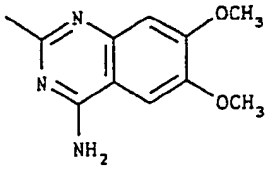
R^1 is amino or 1-pyrrolidinyl;

or a 4-chloro-3-oxo-2,3-dihydro-5-pyridazinyl group of the formula (b);



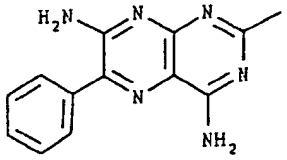
(b)

or a 4-amino-6,7-dimethoxy-2-quinazolinyl group of the formula (c);



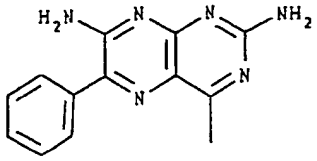
(c)

or a 4,7-diamino-6-phenyl-2-pteridinyl group of the formula (d);



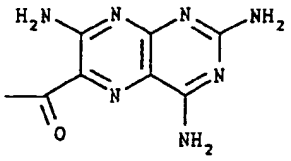
(d)

or a 2,7-diamino-6-phenyl-4-pteridinyl group of the formula (e);



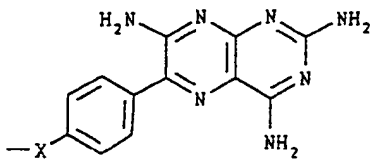
(e)

or a 2,4,7-triamino-6-pteridinylcarbonyl group of the formula (f);



(f)

or a group of the general formula (g);



(g)

wherein

X means oxygen, sulfur or nitrogen optionally substituted by lower alkyl,

with the first proviso that

when Het stands for a group of the general formula (a) and both A^1 and A^2 mean single bonds then Lip may not be hydrogen;

with the second proviso that

when Lip is different from naphthyloxy or oxo-substituted tetrahydronaphthyloxy then A^1 means a single bond;

with the third proviso that

when Lip represents naphthyloxy or oxo-substituted tetrahydronaphthyloxy then A^1 may not be a single bond, as well as with the fourth proviso that

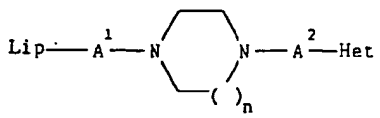
A^1 and A^2 cannot simultaneously stand for C_{2-3} alkylene optionally substituted by hydroxy or oxo,

and their salts.

2. A compound of claim 1 selected from the group consisting of 1-(10-undecenoyl)-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]piperazine, 1-[2-hydroxy-3-(2-naphthyloxy)propyl]-4-[2,6-di(1-pyrrolidinyl)-4-pyrimidinyl]homopiperazine, 6-[4-[2-hydroxy-3-(1-piperazinyl)propoxy]phenyl]-2,4,7-triaminopteridine, 6-[4-[N-methyl-N-[2-hydroxy-3-(1-piperazinyl)propyl]amino]phenyl]-2,4,7-triaminopteridine and the salts thereof.

3. A pharmaceutical composition which comprises as active ingredient one or more compounds of claim 1 or 2, or a pharmaceutically acceptable acid addition salt thereof, optionally in admixture with carriers and/or additives commonly used in the pharmaceutical practice.

4. A process for the preparation of the - compounds of the general formula (I), according to claim 1 or 2,



(I)

wherein

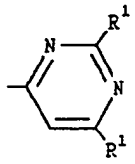
Lip stands for hydrogen; C_{15-20} alkyl; C_{10-20} alkanoyl or C_{10-20} alkenoyl; trityl optionally substituted by halogen; adamantyl; 1- or 2-naphthyloxy or oxo-substituted tetrahydronaphthyloxy; or an amine protective group commonly used e.g. in the peptide chemistry;

A^1 and A^2 are selected independently from the group consisting of a single bond and C_{2-3} alkylene optionally substituted by hydroxy or oxo;

n is 1 or 2; and

Het represents

a group of the general formula (a),

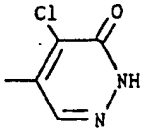


(a)

wherein

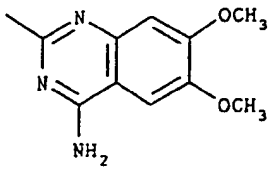
R^1 is amino or 1-pyrrolidinyl;

or a 4-chloro-3-oxo-2,3-dihydro-5-pyridazinyl group of the formula (b);



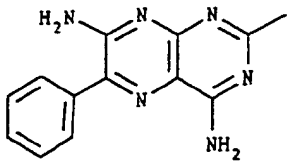
(b)

or a 4-amino-6,7-dimethoxy-2-quinazolinyl group of the formula (c);



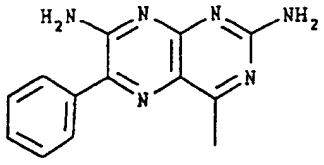
(c)

or a 4,7-diamino-6-phenyl-2-pteridinyl group of the formula (d);



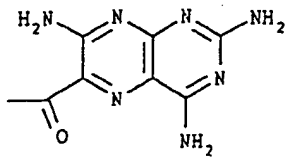
(d)

or a 2,7-diamino-6-phenyl-4-pteridinyl group of the formula (e);



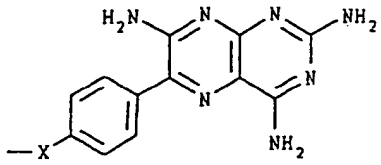
(e)

or a 2,4,7-triamino-6-pteridinylcarbonyl group of the formula (f);



(f)

or a group of the general formula (g);



(g)

wherein

X means oxygen, sulfur or nitrogen optionally substituted by lower alkyl,

with the first proviso that

when Het stands for a group of the general formula (a) and both A^1 and A^2 mean single bonds then Lip may not be hydrogen;

with the second proviso that

when Lip is different from naphthyloxy or oxo-substituted tetrahydronaphthyloxy then A^1 means a single bond;

with the third proviso that

when Lip represents naphthyloxy or oxo-substituted tetrahydronaphthyloxy then A^1 may not be a single bond,

as well as with the fourth proviso that

A^1 and A^2 cannot simultaneously stand for C_{2-3} alkylene optionally substituted by hydroxy or oxo,

and the pharmaceutically acceptable salts thereof, **characterized** in that

a) for preparing compounds of the general formula (I), wherein

Lip is as defined in claim 1, with the proviso that it may not be hydrogen or an amine protective group;

A^1 is as defined in claim 1, with the proviso that when Lip stands for naphthyloxy or oxo-substituted tetrahydronaphthyloxy then it may not be a single bond; and

n, A^2 and Het are as defined in claim 1,

a compound of the general formula (II),

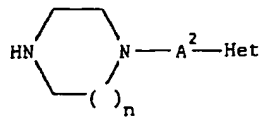
$$Lip\text{-}A^1\text{-}L^1 \quad (II)$$

wherein

Lip and A^1 are as defined above and

L^1 is a leaving group,

is reacted with a compound of the general formula (III),



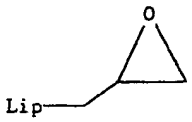
(III)

wherein

n, A^2 and Het are as defined above; or

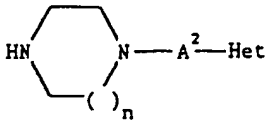
b) for preparing compounds of the general formula (I), wherein

Lip means naphthyloxy or oxo-substituted tetrahydronaphthyloxy;
A^1 stands for 1,3-propylene substituted by hydroxy; and
n, A^2 and Het are as defined in claim 1,
a compound of the general formula (IV),



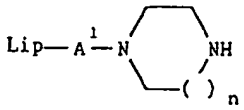
(IV)

wherein
Lip is as defined above,
is reacted with a compound of the general formula (III),



(III)

wherein
n, A^2 and Het are as defined above; or
c) for preparing compounds of the general formula (I), wherein
Lip is as defined in claim 1, with the proviso that it may not be hydrogen;
A^1 is as defined in claim 1, with the proviso that when Lip stands for naphthyloxy or oxo-substituted tetrahydronaphthyloxy then A^1 may not be a single bond; and with the other proviso that when Lip stands for an amine protective group then A^1 is a single bond; and
n, A^2 and Het are as defined in claim 1,
a compound of the general formula (V),



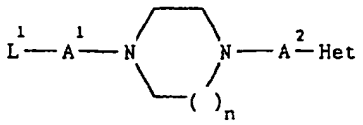
(V)

wherein
Lip, A^1 and n are as defined above,
is reacted with a compound of the general formula (VI),

$$L^2\text{-}A^2\text{-Het}$$

(VI)

wherein
A^2 and Het are as defined above, and
L^2 stands for a leaving group; or
d) for preparing compounds of the general formula (I), wherein
Lip means naphthyloxy or oxo-substituted tetrahydronaphthyloxy;
A^1 is as defined in claim 1, with the proviso that it may not be a single bond; and
n, A^2 and Het are as defined in claim 1,
a compound of the general formula (VII),



(VII)

wherein

A^1, n, A^2 and Het are as defined above, and

L^1 stands for a leaving group,

is reacted with a compound of the general formula Lip-H,

wherein

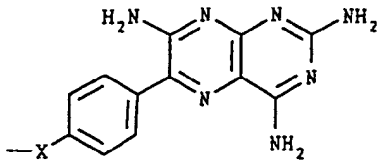
Lip is as defined above; or

e) for preparing compounds of the general formula (I), wherein

Lip is as defined in claim 1, with the proviso that it may not be naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

A^1 is a single bond;

Het stands for a group of the general formula (g),



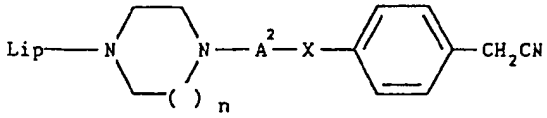
(g)

wherein

X is as defined in claim 1; and

n and A^2 are as defined above,

a compound of the general formula (VIII),



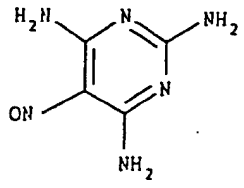
(VIII)

wherein

Lip is as defined above, with the proviso that it may not be hydrogen, naphthyloxy or oxo-substituted tetrahydronaphthyloxy; and

n, X and A^2 are as defined above,

is reacted with 5-nitroso-2,4,6-triaminopyrimidine of the formula (IX),



(IX)

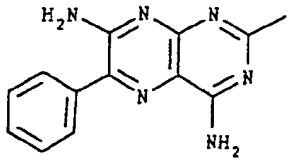
and in the case when Lip stands for an amine protective group, this protective group is removed from the compound thus obtained; or

f) for preparing compounds of the general formula (I), wherein

Lip is as defined in claim 1, with the proviso that it may not be naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

both A^1 and A^2 are single bonds;

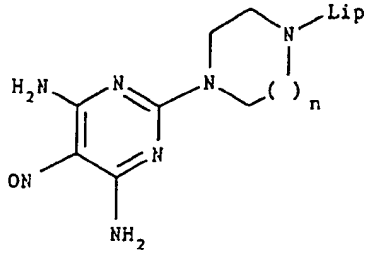
Het stands for a group of the formula (d);



(d)

and n is as defined in claim 1,

a compound of the general formula (X),



(X)

wherein

Lip is as defined above, with the proviso that it may not be hydrogen, naphthyloxy or oxo-substituted tetrahydronaphthyloxy; and

n is as defined above,

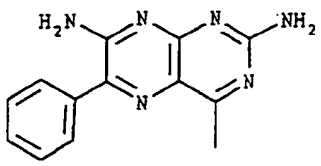
is reacted with benzyl cyanide and in the case when Lip stands for an amine protective group, this protective group is removed from the product thus obtained; or

g) for preparing compounds of the general formula (I), wherein

Lip is as defined in claim 1, with the proviso that it may not be naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

both A^1 and A^2 are single bonds;

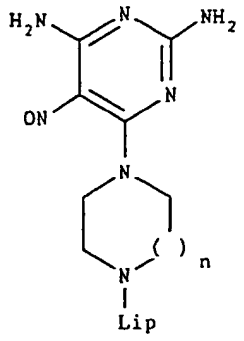
Het stands for a group of the formula (e);



(e)

and n is as defined in claim 1,

a compound of the general formula (XI),



(XI)

wherein

Lip is as defined above, with the proviso that it may not be hydrogen, naphthyloxy or oxo-substituted tetrahydronaphthyloxy, and

n is as defined above,

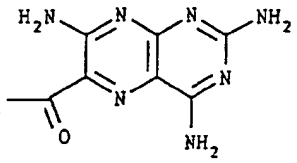
is reacted with benzyl cyanide and in the case, when Lip stands for an amine protective group, this protective group is removed from the product obtained; or

h) for preparing compounds of the general formula (I), wherein

Lip is as defined in claim 1, with the proviso that it may not be naphthyloxy or oxo-substituted tetrahydronaphthyloxy;

both A^1 and A^2 are single bonds;

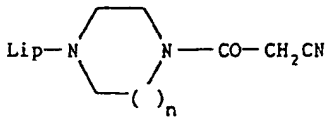
Het stands for a group of the formula (f);



(f)

and n is as defined in claim 1,

a compound of the general formula (XII),



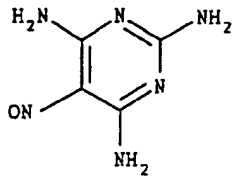
(XII)

wherein

Lip is as defined above, with the proviso that it may not be hydrogen, naphthyloxy or oxo-substituted tetrahydronaphthyloxy, and

n is as defined above,

is reacted with 5-nitroso-2,4,6-triaminopyrimidine of the formula (IX)



(IX)

and in the case, when Lip stands for an amine protective group, this protective group is removed from the product thus obtained,

and, if desired, the compound of the general formula (I) prepared by any of the above processes a) - h) is converted to its acid addition salt.

5. A process for preparing a pharmaceutical composition which comprises mixing as active ingredient one or more compounds of claim 1 or 2, or as prepared in claim 4, or a pharmaceutically acceptable acid addition thereof, with carriers and/or additives commonly used in the pharmaceutical practice.

6. Use of the compounds of claim 1 or 2 or the pharmaceutically acceptable salts thereof for the preparation of medicaments for the treatment of patients suffering from diseases and conditions being in direct or indirect connection with pathological peroxidation processes occuring in the living organism, particularly for the treatment of prevention of diseases and conditions where the inhibition of lipid peroxidation is desirable.